[Attorney Docket: 12013/56301]

OIPE IAP62 FEB 08 2007 PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

OIPE IAP62 FEB 08 2007 PATENT & TRADEMARK OFFICE

Inventor : Maria PALASIS

Serial No.: 09/542,935

Filing Date: April 4, 2000

For: Insertable or Implantable Medical Devices Suitable for Gene Therapy Regimens

Art Unit : 1635

Examiner : B. A. Whiteman

Mail Stop Petition
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PETITION UNDER 37 C.F.R. §1.181(a)(1)

S I R:

Petitioner hereby requests that the pending claims of U.S. Patent Application Serial No. 09/542,935 ("the present application") be granted the priority date of U.S. Patent Application Serial No. 09/204,254 (now U.S. Patent No. 6,369,039; "the '039 patent").

Exhibit A contains a copy of pending claims 60, 62, and 65-91 of the present application. Exhibit B is a copy of the '039 patent.

Background

The Office Action dated August 15, 2006, a copy of which is Exhibit C, stated that the pending claims are not entitled to the priority date of the '039 patent. The Office Action provided two reasons for this conclusion:

(1) The '039 patent does not contain a written description of the subgenus of angiogenic agents supposedly set forth in the claims. See Exhibit C, paragraph bridging pages 2-3:

> However, the list set forth in the new claims does not include all of the products listed in the specification [of the ''039 patent] that are considered angiogenic agents (e.g., hif-1). The specification [of the ''039 patent] does not disclose the subgenus set [sic, forth?] in the new claims and claims dependent therefrom. Thus, nothing in the specification [of the '039 patent] would lead one to the particular combination set forth in the amended and claims dependent therefrom and new claims [sic].

(2) All the pending claims recite a combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent. The Office Action argued that there is no disclosure in the '039 patent of the use of both an angiogenic agent and a polynucleotide encoding an angiogenic agent. Instead, according to the Office Action, the '039 patent only discloses the use of either an angiogenic agent or a polynucleotide encoding an angiogenic agent. See, e.g., Exhibit C, page 3, second paragraph from bottom:

> [W]hile it is acknowledged that acidic or basic fibroblast growth factor or DNA encoding acidic or basic fibroblast growth factor is listed in col. 5, line 66 [of the '039 patent], the limitation is directed to either acidic or basic fibroblast growth factor or DNA encoding acidic or basic fibroblast growth factor. The limitation does not embrace using an acidic or basic fibroblast growth factor and DNA encoding either factor. There is nothing in the specification of '039 to lead the skilled artisan to using both in the medical device.

In an Amendment dated November 10, 2006, a copy of which is Exhibit D, the Applicant asked for reconsideration of the denial of priority and responded to reason (1) by pointing out that the pending claims do not contain a list of angiogenic agents that is a subgenus of any lists disclosed in Exhibit B and responded to reason (2) by presenting arguments as to why the pending claims were entitled to priority from Exhibit B.

In an Advisory Action dated December 8, 2006, a copy of which is Exhibit E, the Examiner reaffirmed the denial of priority by reasserting reason (2).

This Petition is being filed within two months of the reaffirmation of the denial of priority in Exhibit E and thus is timely.

The pending claims

The currently pending claims were added by an Amendment filed November 17, 2005, a copy of which is Exhibit F. An Advisory Action dated December 12, 2005, a copy of which is Exhibit G, stated that these claims were not entered. In response, the Applicant filed a Request for Continued Examination on February 1, 2006, a copy of which is Exhibit H, together with a copy of Exhibit F and asked that Exhibit F be entered. The Request for Continued Examination was granted in an Office Action dated March 6, 2006, a copy of which is Exhibit I. In Exhibit I, it was stated that Exhibit F had been entered (see page 2 of Exhibit I).

Accordingly, the pending claims are those submitted in Exhibit F, a clean copy of which is Exhibit A.

The merits of the denial of priority

The combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent is disclosed in Exhibit B in the paragraph at col. 5, l. 49 to col. 6, l. 22:

> Polynucleotide sequences useful in practice of the invention include DNA or RNA sequences having a therapeutic effect after being taken up by a cell. Examples of therapeutic polynucleotides include anti-sense DNA and RNA; DNA coding for an anti-sense RNA; or DNA coding for tRNA or rRNA to replace defective or deficient endogenous molecules. The polynucleotides of the invention can also code for therapeutic polypeptides. A polypeptide is understood to be any translation product of a polynucleotide regardless of size, and whether glycosylated or not. Therapeutic polypeptides include as a primary example, those polypeptides that can compensate for defective or deficient species in an animal, or those that act through toxic effects to limit or remove harmful cells from the body. In addition, the polypeptides or proteins that can be incorporated into the polymer coating **130**, or whose DNA can be incorporated, include without limitation, angiogenic factors including acidic and basic fibroblast growth factors, vascular endothelial growth factor, epidermal growth factor, transforming growth factor α and β, platelet-derived enotheial growth factor, platelet-derived growth factor, tumor necrosis factor α, hepatocyte growth factor and insulin like growth factor; growth factors; cell cycle inhibitors including CDK inhibitors; thymidine kinase ("TK") and other agents useful for interfering with cell proliferation, including agents for treating malignancies; and combinations thereof. Still other useful factors, which can be provided as polypeptides or as DNA encoding these polypeptides, include monosite chemoattractant protein ("MCP-1"), and the family of bone morphogenic proteins ("BMP's"). The known proteins include BMP-2, BMP-3, BMP-4, BMP-5, BMP-6 (Vgr-1), BMP-7 (OP-1), BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, BMP-14, BMP-15, and BMP-16. Currently preferred BMP's are any of BMP-2, BMP-3, BMP-4, BMP-5, BMP-6 and BMP-7. These dimeric proteins can be provided as homodimers, heterodimers, or combinations thereof, alone or together with other molecules. Alternatively or, in addition, molecules capable of inducing an upstream or downstream effect of a BMP can be provided. Such molecules include any of the "hedgehog" proteins, or the DNA's encoding them.

In this passage, Exhibit B first makes clear that the polymeric coating of the devices described therein can include polynucleotides encoding therapeutic agents ("Polynucleotide sequences useful in practice of the invention include DNA or RNA sequences having a therapeutic effect after being taken up by a cell;" col. 5, ll. 49-51). Exhibit B then states that, **in addition to** the polynucleotides, the polymeric coating may contain polypeptides and proteins ("In addition, the polypeptides or proteins that can be incorporated into the

polymeric coating ... ;" col. 5, ll. 62-64). This is followed by a list of suitable therapeutic agents, including the angiogenic agents that are recited in the present claims.

The combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent is also disclosed in the paragraph at col. 4, l. 64 to col. 5, l. 48:

> The therapeutic agents used in the present invention include, for example, pharmaceutically active compounds, proteins, oligonucleotides, ribozymes, anti-sense genes, DNA compacting agents, gene/vector systems (i.e., anything that allows for the uptake and expression of nucleic acids), nucleic acids (including, for example, recombinant nucleic acids; naked DNA, cDNA, RNA; genomic DNA, CDNA or RNA in a non-infectious vector or in a viral vector which may have attached peptide targeting sequences; antisense nucleic acid (RNA or DNA); and DNA chimeras which include gene sequences and encoding for ferry proteins such as membrane translocating sequences ("MTS") and herpes simplex virus-1 ("VP22")), and viral, liposomes and cationic polymers that are selected from a number of types depending on the desired application. For example, biologically active solutes include anti-thrombogenic agents such as heparin, heparin derivatives, urokinase, PPACK (dextrophenylalanine proline arginine chloromethylketone), rapamycin, probucol, and verapimil; angiogenic and anti-angiogenic agents; anti-proliferative agents such as enoxaprin, angiopeptin, or monoclonal antibodies capable of blocking smooth muscle cell proliferation, hirudin, and acetylsalicylic acid; anti-inflammatory agents such as dexamethasone, prednisolone, corticosterone, budesonide, estrogen, sulfasalazine, and mesalamine; antineoplastic/antiproliferative/anti-mitotic agents such as paclitaxel, 5-fluorouracil, cisplatin, vinblastine, vincristine, epothilones, endostatin, angiostatin and thymidine kinase inhibitors; anesthetic agents such as lidocaine, bupivacaine, and ropivacaine; anti-coagulants such as D-Phe-Pro-Arg chloromethyl keton, an RGD peptide-containing compound, heparin, antithrombin compounds, platelet receptor antagonists, anti-thrombin anticodies, anti-platelet receptor antibodies, aspirin, prostaglandin inhibitors, platelet inhibitors and tick antiplatelet factors; vascular cell growth promoters such as growth factors, growth factor receptor antagonists, transcriptional activators, and translational promoters; vascular cell growth inhibitors such as growth factor inhibitors, growth factor receptor antagonists, transcriptional repressors, translational repressors, replication inhibitors, inhibitory antibodies, antibodies directed against growth factors, bifunctional molecules consisting of a growth factor and a cytotoxin, bifunctional molecules consisting of an antibody and a cytotoxin; cholesterol-lowering agents; vasodilating agents; agents which interfere with endogeneus vascoactive mechanisms; survival genes which protect against cell death, such as anti-apoptotic Bcl-2 family factors and Akt kinase; and combinations thereof. These and other compounds are added to the polymer coating using similar methods and routinely tested as set forth in the specification. Any modifications are routinely made by one skilled in the art.

This paragraph teaches that polynucleotides (col. 4, l. 67, to col. 5, l. 4) and angiogenic agents (col. 5, ll. 15-16) can be in the polymeric coating. It is then stated that combinations of polynucleotides and angiogenic agents can be in the coating ("and combinations thereof;" col. 5, l. 44). That the polynucleotides may encode angiogenic agents is taught at col. 5, ll. 62-65.

In view of the disclosures of Exhibit B discussed above, the pending claims are therefore entitled to the priority date of U.S. Patent Application Serial No. 09/204,254 (now U.S. Patent No. 6,369,039).

Accordingly, it is respectfully requested that the denial of priority be reversed.

The Petitioner hereby makes a Conditional Petition for any relief available to correct any defect seen in connection with this filing, or any defect seen to be remaining in this application after this filing. The Commissioner is authorized to charge Kenyon & Kenyon's Deposit Account No. 11-0600 for any fees associated with such Conditional Petition.

Respectfully submitted,
KENYON & KENYON LLP

FEBRUARY 8, 2007
Date

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02-12-07

[12013/56301]

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	Maria PALASIS	Group Art Unit: 1635
Serial No.:	09/542,935	Examiner: B. A. Whiteman
Filing Date:	April 4, 2000	
For:	INSERTABLE OR IMPLANTABLE MEDICAL DEVICES SUITABLE FOR GENE THERAPY REGIMENS	

Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

TRANSMITTAL FOR PETITION UNDER 37 C.F.R. § 1.181(a)(1)

SIR:

Transmitted herewith is a Petition under 37 C.F.R. § 1.181(a)(1) in connection with the above-captioned application.

Please note additionally enclosed which accompany this response are the following:

Exhibits A through I.

It is believed that no fees are required in connection with this Petition. However, if any fees are required in connection with this Petition, the Commissioner is hereby authorized to charge any and all such fees to the deposit account of KENYON & KENYON LLP, Deposit Account No. 11 0600. A duplicate copy of this transmittal letter is enclosed for that purpose.

Respectfully submitted,

Dated: February 8, 2007

By: Joseph A Coppola
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Pending claims

60. A medical device comprising:

a biocompatible structure comprising a polymeric coating that coats at least a portion of said structure, said polymeric coating comprising:

(A) a therapeutic agent, wherein said therapeutic agent is an angiogenic agent, and

(B) a vector containing a polynucleotide that establishes a gene expression sufficient to produce a therapeutically sufficient amount of one or more products encoded by said polynucleotide, wherein said polynucleotide encodes a polypeptide or protein, wherein said polypeptide or protein is an angiogenic agent.

62. A method of controlled delivery of a genetic material to a mammalian body comprising:

(A) applying a polymer coating to at least a portion of a medical device;

(B) applying a genetic material to said polymer coating to obtain a genetically coated medical device, said genetic material comprising:

(1) a therapeutic agent, wherein said therapeutic agent is an angiogenic agent,

and

(2) a vector containing a polynucleotide that establishes a gene expression sufficient to produce a therapeutically sufficient amount of one or more products encoded by said polynucleotide, wherein said polynucleotide encodes a polypeptide or protein, wherein said polypeptide or protein is an angiogenic agent,

and

(C) inserting or implanting said genetically coated medical device at a predetermined site in said mammal.

65. The medical device of claim 60, wherein said vector is a viral vector.

66. The medical device of claim 65, wherein said vector is an adenoassociated virus vector.

67. The medical device of claim 60, wherein said polymeric coating comprises polyurethane, silicone, EVA, poly-l-lactic acid /poly ϵ-caprolactone blends, or a combination thereof.

68. The medical device of claim 60, wherein said polymer coating is from about 1 to about 40 layers having a thickness of from about 1 to about 10 μm/ layer of coating.

69. The medical device of claim 60, wherein said structure is a stent.

70. The medical device of claim 69, wherein said stent is a metallic stent.

71. The medical device of claim 60, wherein said angiogenic agent is acidic or basic fibroblast growth factor.

72. The medical device of claim 60, wherein said angiogenic agent is vascular endothelial growth factor.

73. The medical device of claim 60, wherein said angiogenic agent is platelet-derived growth factor.

74. The medical device of claim 60, wherein said angiogenic agent is platelet-derived endothelial growth factor.

75. The medical device of claim 60, wherein said angiogenic agent is epidermal growth factor.

76. The medical device of claim 60, wherein said angiogenic agent is transforming growth factor α or β.

77. The medical device of claim 60, wherein said angiogenic agent does not include nitric oxide synthase.

78. A method of inhibiting or treating restenosis in a patient, said method comprising administering at a predetermined site within the body of said patient the device of claim 60.

79. The method of claim 78, wherein said site is a site of mechanical injury to an arterial wall produced by treatment of an atherosclerotic lesion by angioplasty.

80. The method of claim 62, wherein said vector is a viral vector.

81. The method of claim 80, wherein said vector is an adenoassociated virus vector.

82. The method of claim 62, wherein said polymeric coating comprises polyurethane, silicone, EVA, poly-l-lactic acid /poly ϵ-caprolactone blends, or a combination thereof.

83. The method of claim 62, wherein said polymer coating is from about 1 to about 40 layers having a thickness of from about 1 to about 10 μm/ layer of coating.

84. The method of claim 62, wherein said structure is a stent.

85. The method of claim 84, wherein said stent is a metallic stent.

86. The method of claim 62, wherein said angiogenic agent is acidic or basic fibroblast growth factor.

87. The method of claim 62, wherein said angiogenic agent is vascular endothelial growth factor.

88. The method of claim 62, wherein said angiogenic agent is platelet-derived growth factor.

89. The method of claim 62, wherein said angiogenic agent is platelet-derived endothelial growth factor.

90. The method of claim 62, wherein said angiogenic agent is epidermal growth factor.

91. The method of claim 62, wherein said angiogenic agent does not include nitric oxide synthase.

US006369039B1

(12) **United States Patent**
Palasis et al.

(10) **Patent No.: US 6,369,039 B1**
(45) **Date of Patent: Apr. 9, 2002**

(54) **HIGH EFFICIENCY LOCAL DRUG DELIVERY**

(75) Inventors: **Maria Palasis**, Wellesley; **Kenneth Walsh**, Carlisle, both of MA (US)

(73) Assignee: **Scimed Life Sytems, Inc.**, Maple Grove, MN (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/204,254**

(22) Filed: **Dec. 3, 1998**

Related U.S. Application Data

(63) Continuation-in-part of application No. 09/106,855, filed on Jun. 30, 1998, now abandoned.

(51) **Int. Cl.**[7] **A61K 48/00**

(52) **U.S. Cl.** **514/44**; 514/2; 424/93.2; 604/51; 604/52; 604/53

(58) **Field of Search** 514/44, 449, 411, 514/1, 2, 84; 604/265; 424/93.2; 435/320.1, 455

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Primary Examiner—Dave T. Nguyen
(74) *Attorney, Agent, or Firm*—Kenyon & Kenyon

(57) **ABSTRACT**

A method of site-specifically delivering a therapeutic agent to a target location within a body cavity, vasculature or tissue. The method comprises the steps of providing a medical device having a substantially saturated solution of therapeutic agent associated therewith; introducing the medical device into the body cavity, vasculature or tissue; releasing a volume of the solution of therapeutic agent from the medical device at the target location at a pressure of from about 0 to about 5 atmospheres for a time of up to about 5 minutes; and withdrawing the medical device from the body cavity, vasculature or tissue. In another aspect, the present invention includes a system for delivering a therapeutic agent to a body cavity, vasculature or tissue, comprising a medical device having a substantially saturated solution of the therapeutic agent associated therewith.

19 Claims, 2 Drawing Sheets

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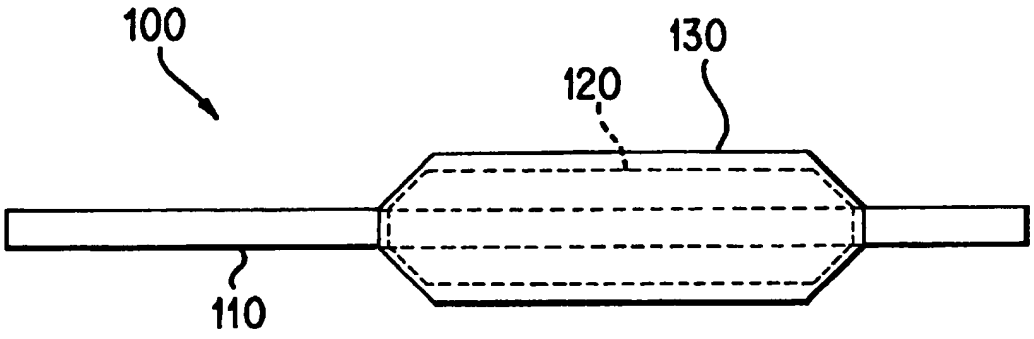

FIG. 1

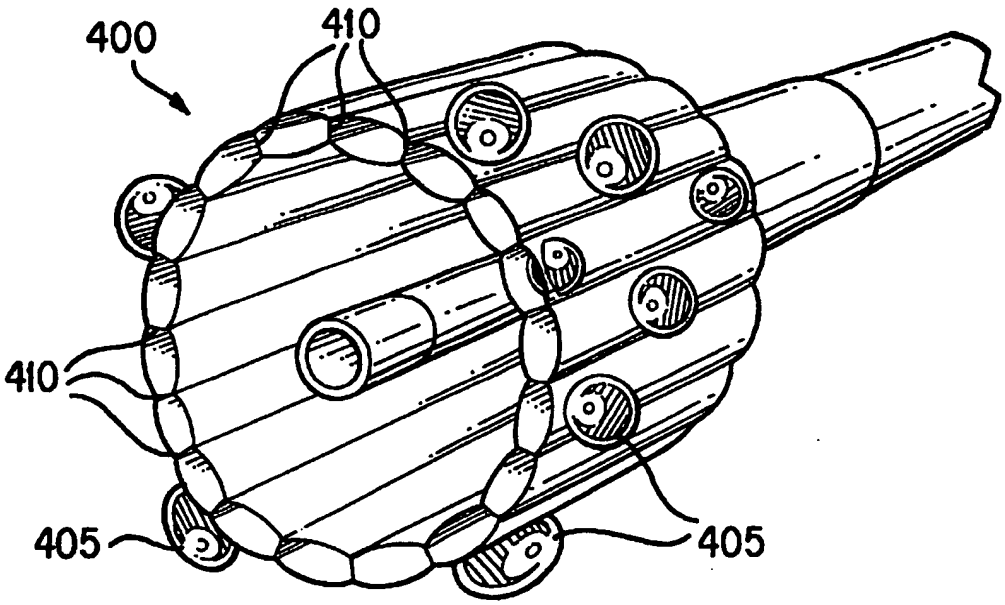

FIG. 2

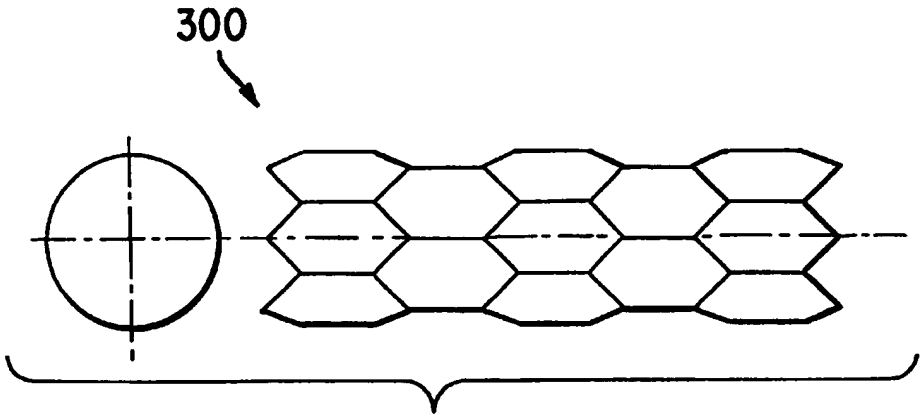

FIG. 3

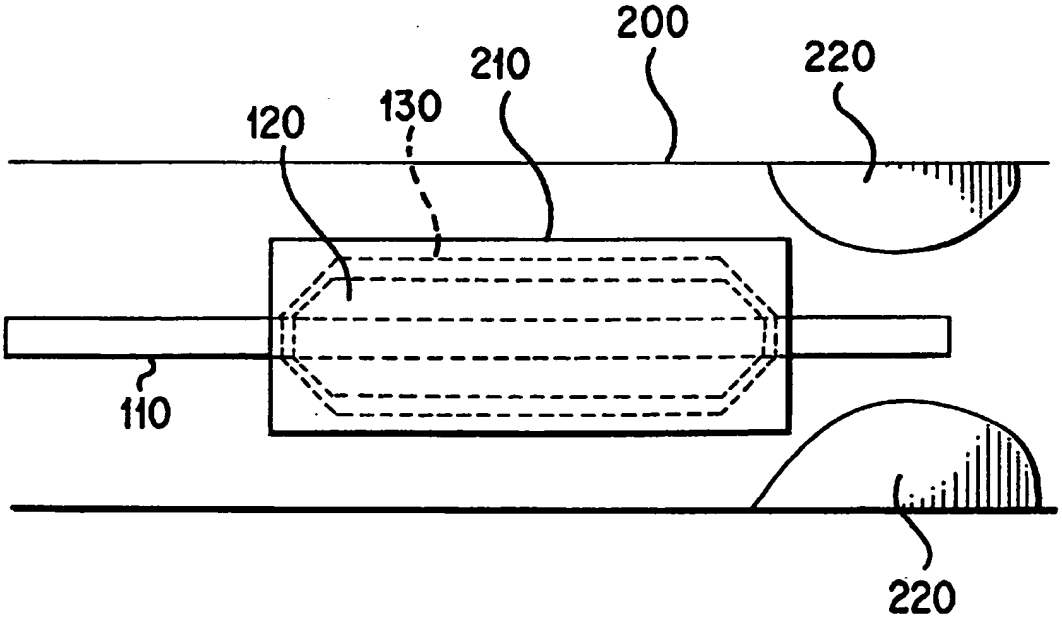

FIG. 4

HIGH EFFICIENCY LOCAL DRUG DELIVERY

The present application is a continuation-in-part of application Ser. No. 09/106,855, filed Jun. 30, 1998, abandoned.

FIELD OF THE INVENTION

The present invention relates to the site-specific delivery of therapeutic agents to target locations within body cavities, vasculatures, or tissues.

BACKGROUND

The treatment of disease such as vascular disease by local pharmacotherapy presents a means of delivering therapeutic drug doses to target tissues while minimizing systemic side effects. Recently, for example, the local delivery of gene constructs to effect vascular response has gained increased interest. Gene transfection of vascular smooth muscle cells in vivo, however, remains a problem due to low transfer efficiency attributed in part to inefficient local delivery devices and to the barrier properties of the vessel wall.

As an example of localized delivery of therapeutic agents, in vivo adenoviral gene transfer has been accomplished with the use of site-specific delivery catheters. Independent of the local delivery device used, most studies have delivered viral doses ranging from 1×10^9 to 1×10^{10} pfu/ml over extended delivery times of 20 minutes or longer, and typically in delivery volumes of 1 ml or more. Although these conditions are widely used, the lack of optimization studies with local delivery devices suggests that delivery conditions are not necessarily optimal. Moreover, conventional localized techniques are often invasive in that they typically involve side branch ligation, long delivery times, and when the delivery device is an expandable device such as a balloon catheter, these techniques usually are associated with high pressures to accomplish drug delivery. Localized delivery techniques making use of long delivery times and high pressures and volumes often result in tissue damage, ischemia and other problems. Attempts have been made to reduce the delivery time from an infusion based device using a polymer carrier such as Poloxamer (BASF Corporation), whereby delivery times are reduced from 30 minutes to 5 minutes. The clinical utility of this approach, however, remains uncertain.

SUMMARY OF THE INVENTION

In one aspect, the present invention includes a method of site-specifically delivering a therapeutic agent to a target location within a body cavity, vasculature or tissue. The method comprises the steps of providing a medical device having a substantially saturated solution of therapeutic agent associated therewith; introducing the medical device into the body cavity, vasculature or tissue; releasing a volume of the solution of therapeutic agent from the medical device at the target location at a pressure of from about 0 to about 5 atmospheres for a time of up to about 5 minutes; and withdrawing the medical device from the body cavity, vasculature or tissue.

In another aspect, the present invention includes a system for delivering a therapeutic agent to a body cavity, vasculature or tissue, comprising a medical device having a substantially saturated solution of the therapeutic agent associated therewith.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows a medical device in accordance with an embodiment of the present invention.

FIG. 2 shows a cross-section of an infusion catheter used in accordance with an embodiment of the present invention.

FIG. 3 shows a stent used in accordance with an embodiment of the present invention.

FIG. 4 shows a medical device being positioned to a target location within a body lumen, in accordance with an embodiment of the present invention.

DETAILED DESCRIPTION

The present invention overcomes the deficiencies of conventional localized drug delivery techniques by providing a site-specific, minimally-invasive method of delivering therapeutic agents to tissue. The method of the present invention advantageously makes use of low delivery pressures and short delivery durations to provide for the quick and safe localized delivery of therapeutic agents to any suitable lumen, cavity, or tissue in the body such as, for example, blood vessels, heart tissue, and locations within the gastrointestinal tract and urological and gynecological systems. The terms "drug" and "therapeutic agent" are used interchangeably herein and include pharmaceutically active compounds, nucleic acids with and without carrier vectors such as lipids, compacting agents (such as histones), virus, polymers, proteins, and the like, with or without targeting sequences.

In the localized delivery of therapeutic agents, pressure-driven convection and concentration-driven diffusion are the two predominant transport mechanisms in the target tissue. The relative importance of these mechanisms, however, has previously not been well-understood. Convective flow is defined as fluid flow through a solvent space due to a pressure difference acting across a region of tissue. Convective solute transport occurs when dissolved solutes are carried along with the fluid flow. Although small molecules are generally easily convected with the fluid flow, a sieving effect by the tissue tends to retard large molecules. In contrast to convective transport, molecular diffusion is defined as solute transport from regions of high concentration to regions of low concentration due to random molecular motions. Transport due to molecular diffusion is directly proportional to an applied concentration gradient.

The inventors have surprisingly discovered that under appropriate conditions, therapeutic agents are transported into tissue in a manner consistent with molecular diffusion. Correspondingly, the inventors have surprisingly found that variations in applied pressure during localized drug administration has no significant effect on the transport of drug agents or other therapeutic agents into target tissue. The present invention makes use of this finding by providing for drug delivery based on the principles of concentration-driven diffusion. Delivery of therapeutic agents is thus achieved by controlling the concentration of therapeutic agent at a target location, rather than relying on pressure-driven processes.

In one aspect, the present invention includes a method of site-specifically delivering a therapeutic agent to a target location within a body cavity, vasculature or tissue of a mammal. The method comprises the steps of providing a medical device having a substantially saturated solution of therapeutic agent associated therewith; introducing the medical device into the body cavity, vasculature, or tissue sought to be treated; releasing the solution of therapeutic agent from the medical device at the target location at a pressure of from about 0 to about 5 atmospheres; and withdrawing the medical device from the target location within about 5 minutes from the time of releasing the solution from the medical device.

To achieve high efficiency drug delivery by concentration-driven molecular diffusion, the therapeutic agent is incorporated into the medical device as a substantially saturated solution. As used herein, "substantially saturated solution" means that the concentration of dissolved therapeutic agent in a solvent, such as water or another physiologically acceptable carrier, is at least about 75%, preferably at least about 80%, 85%, 90%, 95% or 100% of the limit of solubility of the therapeutic agent in the solvent. Alternatively, the concentration of the therapeutic agent is limited by the concentration that results in an undesirable toxic response from a patient. The substantially saturated solution is "associated with" the medical device in that the therapeutic agent is held in a cavity(ies) of the device, such as in an infusion style catheter such as a channel balloon catheter; or the therapeutic agent is coated onto the surface of the device as a coating per se or as part of a coating; or the substantially saturated solution is held within or passes through the medical device, such as in a needle injection catheter.

The present invention is described herein with specific reference to an expandable catheter as the medical device. Other medical devices within the scope of the present invention include implantable devices such as needle injection catheters, hypodermic needles, stents, blood clot filters, vascular grafts, stent grafts, aneurysm filling coils, trans myocardial revascularization ("TMR") devices, percutaneous myocardial revascularization ("PMR") devices etc., as are known in the art.

The catheter used with the present invention is any suitable catheter such as, for example, an infusion catheter (such as a channeled balloon catheter as described in U.S. Pat. No. 5,254,089, incorporated herein by reference, transport catheter, or microporous balloon catheter), an angioplasty balloon catheter, a double balloon catheter, or an infusing sleeve catheter, as are known in the art. The therapeutic agent is applied to, or is incorporated into, the expandable portion of such catheters. For example, the therapeutic agent is included as part of a polymer coating that is applied to said expandable portions. Alternatively, the therapeutic agent is incorporated directly into the expandable portion. Alternatively, the therapeutic agent is introduced into the catheter after the catheter is positioned to the target tissue by infusing the therapeutic agent through the infusion port of an-infusion catheter.

In accordance with the present invention, once the catheter is positioned at the target location, the therapeutic agent is released at a pressure of not more than about 5 atmospheres, preferably not more than about 1 atmosphere, and more preferably, not more than about 0.1 atmosphere. The catheter is held at the target site for therapeutic agent delivery for a duration of not more than about 5 minutes, preferably not more than about 2 minutes, and more preferably not more than about 1 minute. Because the present invention makes use of concentration-driven molecular diffusion rather than pressure-driven convention for the delivery of therapeutic agents, it allows for low delivery pressures and durations not heretofore known in the art. The delivery techniques of the present invention thus minimize the risk of tissue damage, ischemia, etc., commonly associated with conventional localized delivery techniques.

With specific reference to FIG. **1**, the delivery of a therapeutic agent to a target location is accomplished with the use of a medical device **100** comprising a catheter **110** having an expandable portion **120**. The expandable portion **120** of the catheter **110** is optionally coated with a polymer for holding the therapeutic agent during delivery into the body. The polymer coating **130** is preferably capable of absorbing a substantial amount of drug solution. The polymer coating **130** is placed onto the expandable portion **120** by any suitable mean such as, for example, by immersion, spraying, or deposition by plasma or vapor deposition. The polymer is typically applied to a thickness of about 1 to 30 microns, preferably about 2 to 5 microns. Very thin polymer coatings, e.g., of about 0.2–0.3 microns and much thicker coatings, e.g., more than 30 microns, are also possible. It is also within the scope of the present invention to apply multiple layers of polymer coating onto the expandable portion **120** of catheter **110**. Such multiple layers can be of the same or different polymer materials, and may perform different functions (e.g., for biocompatibility, to control drug release, etc.).

The polymer coating **130** comprises any polymeric material capable of absorbing or otherwise holding the therapeutic agent to be delivered. The polymeric material is, for example, hydrophilic, hydrophobic, and/or biodegradable, and is preferably selected from the group consisting of polycarboxylic acids, cellulosic polymers, gelatin, polyvinylpyrrolidone, maleic anhydride polymers, polyamides, polyvinyl alcohols, polyethylene oxides, glycosaminoglycans, polysaccharides, polyesters, polyurethanes, silicones, polyorthoesters, polyanhydrides, polycarbonates, polypropylenes, polylatic acids, polyglycolic acids, polycaprolactones, polyhydroxybutyrate valerates, polyacrylamides, polyethers, and mixtures and copolymers thereof. Coatings from polymer dispersions such as polyurethane dispersions (BAYHDROL, etc.) and acrylic latex dispersions are also within the scope of the present invention. Preferred polymers include polyacrylic acid as described in U.S. Pat. No. 5,091,205, the disclosure of which is incorporated herein by reference; and aqueous coating compositions comprising an aqueous dispersion or emulsion of a polymer having organic acid functional groups and a polyfunctional crosslinking agent having functional groups capable of reacting with organic acid groups, as described in U.S. Pat. No. 5,702,754, the disclosure of which is incorporated herein by reference.

The therapeutic agent is introduced onto the expandable portion **120**, or alternatively, into the polymer coating **130**, by any suitable method. For example, the therapeutic agent is placed in solution, which is thereafter applied to the expandable portion **120** or polymer coating **130** by any suitable means, including dipping into the drug solution or applying the solution by pipet or spraying. In the former method, the amount of drug loading is controlled by regulating the time the polymer coating **130** is immersed in the drug solution, the extent of polymer coating cross-linking, the interactions between the polymer and drug (i.e., bonding, Van der Waals forces, charge interactions, etc.), the concentration of the drug in the solution and/or the amount of polymer coating **130**. In another embodiment of the invention, the drug is incorporated directly into the polymer used in the polymer coating **130** prior to the application of the polymer as a coating onto a medical device. When the medical device used in the present invention is an infusion catheter **400**, such as that shown in cross-section in FIG. **2**, the substantially saturated solution of therapeutic agent (shown in FIG. **2** as **405**) is not coated onto the catheter, but rather is delivered to the target tissue by infusing through the channels **410** of the infusion catheter **400**.

The therapeutic agents used in the present invention include, for example, pharmaceutically active compounds, proteins, oligonucleotides, ribozymes, anti-sense genes, DNA compacting agents, gene/vector systems (i.e., anything

that allows for the uptake and expression of nucleic acids), nucleic acids (including, for example, recombinant nucleic acids; naked DNA, cDNA, RNA; genomic DNA, CDNA or RNA in a non-infectious vector or in a viral vector which may have attached peptide targeting sequences; antisense nucleic acid (RNA or DNA); and DNA chimeras which include gene sequences and encoding for ferry proteins such as membrane translocating sequences ("MTS") and herpes simplex virus-1 ("VP22")), and viral, liposomes and cationic polymers that are selected from a number of types depending on the desired application. For example, biologically active solutes include anti-thrombogenic agents such as heparin, heparin derivatives, urokinase, PPACK (dextrophenylalanine proline arginine chloromethylketone), rapamycin, probucol, and verapimil; angiogenic and anti-angiogenic agents; anti-proliferative agents such as enoxaprin, angiopeptin, or monoclonal antibodies capable of blocking smooth muscle cell proliferation, hirudin, and acetylsalicylic acid; anti-inflammatory agents such as dexamethasone, prednisolone, corticosterone, budesonide, estrogen, sulfasalazine, and mesalamine; antineoplastic/antiproliferative/anti-mitotic agents such as paclitaxel, 5-fluorouracil, cisplatin, vinblastine, vincristine, epothilones, endostatin, angiostatin and thymidine kinase inhibitors; anesthetic agents such as lidocaine, bupivacaine, and ropivacaine; anti-coagulants such as D-Phe-Pro-Arg chloromethyl keton, an RGD peptide-containing compound, heparin, antithrombin compounds, platelet receptor antagonists, anti-thrombin anticodies, anti-platelet receptor antibodies, aspirin, prostaglandin inhibitors, platelet inhibitors and tick antiplatelet factors; vascular cell growth promoters such as growth factors, growth factor receptor antagonists, transcriptional activators, and translational promoters; vascular cell growth inhibitors such as growth factor inhibitors, growth factor receptor antagonists, transcriptional repressors, translational repressors, replication inhibitors, inhibitory antibodies, antibodies directed against growth factors, bifunctional molecules consisting of a growth factor and a cytotoxin, bifunctional molecules consisting of an antibody and a cytotoxin; cholesterol-lowering agents; vasodilating agents; agents which interfere with endogeneus vascoactive mechanisms; survival genes which protect against cell death, such as anti-apoptotic Bcl-2 family factors and Akt kinase; and combinations thereof. These and other compounds are added to the polymer coating using similar methods and routinely tested as set forth in the specification. Any modifications are routinely made by one skilled in the art.

Polynucleotide sequences useful in practice of the invention include DNA or RNA sequences having a therapeutic effect after being taken up by a cell. Examples of therapeutic polynucleotides include anti-sense DNA and RNA; DNA coding for an anti-sense RNA; or DNA coding for tRNA or rRNA to replace defective or deficient endogenous molecules. The polynucleotides of the invention can also code for therapeutic polypeptides. A polypeptide is understood to be any translation product of a polynucleotide regardless of size, and whether glycosylated or not. Therapeutic polypeptides include as a primary example, those polypeptides that can compensate for defective or deficient species in an animal, or those that act through toxic effects to limit or remove harmful cells from the body. In addition, the polypeptides or proteins that can be incorporated into the polymer coating **130**, or whose DNA can be incorporated, include without limitation, angiogenic factors including acidic and basic fibroblast growth factors, vascular endothelial growth factor, epidermal growth factor, transforming growth factor α and β, platelet-derived enotheial growth factor, platelet-derived growth factor, tumor necrosis factor α, hepatocyte growth factor and insulin like growth factor; growth factors; cell cycle inhibitors including CDK inhibitors; thymidine kinase ("TK") and other agents useful for interfering with cell proliferation, including agents for treating malignancies; and combinations thereof. Still other useful factors, which can be provided as polypeptides or as DNA encoding these polypeptides, include monosite chemoattractant protein ("MCP-1"), and the family of bone morphogenic proteins ("BMP's"). The known proteins include BMP-2, BMP-3, BMP-4, BMP-5, BMP-6 (Vgr-1), BMP-7 (OP-1), BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, BMP-14, BMP-15, and BMP-16. Currently preferred BMP's are any of BMP-2, BMP-3, BMP-4, BMP-5, BMP-6 and BMP-7. These dimeric proteins can be provided as homodimers, heterodimers, or combinations thereof, alone or together with other molecules. Alternatively or, in addition, molecules capable of inducing an upstream or downstream effect of a BMP can be provided. Such molecules include any of the "hedgehog" proteins, or the DNA's encoding them.

In one exemplary embodiment of the present invention, the medical device has recombinant nucleic acid incorporated therein, wherein the recombinant nucleic acid comprises a viral vector having linked thereto an exogenous nucleic acid sequence. "Exogenous nucleic acid sequence" is used herein to mean a sequence of nucleic acids that is exogenous to the virus from which the vector is derived. The concentration of the viral vector, preferably an adenoviral vector, is at least about 10^{10} plaque forming units ("p.f.u.") per milliliter ("ml"), preferably at least about 10^{11} p.f.u. per ml. Alternatively, the concentration of the viral vector is limited by the concentration that results in an undesirable immune response from a patient.

After the therapeutic agent is incorporated into the inflatable portion **120** or coating **130**, the medical device **100** is introduced into the body and positioned to a target location through a body cavity or vasculature (e.g., coronary arteries, portal vein, ileofemoral vein, etc.) by torquing or other known techniques. Once the medical device **100** is positioned to a target location within the body, the expandable portion **120** is optionally expanded and the drug is released at a pressure of not more than about 5 atmospheres, preferably not more than about 1 atmosphere, and more preferably, not more than about 0.1 atmosphere. The medical device **100** is held at the target location for a duration of not more than about 5 minutes, preferably not more than about 2 minutes, and more preferably not more than about 1 minute. After delivery, the medical device **100** is removed from the body by known techniques.

In one embodiment, the medical device **100** of the present invention includes a stent **300** (FIG. **3**) for placement in a body lumen. The present invention can thus be used for the dual purpose of localized drug delivery and stent placement. As known in the art, stents are tubular support structures that are implanted inside tubular organs, blood vessels or other tubular body lumens. The stent used with the present invention is of any suitable design, and is either self-expanding or balloon-expandable. The stent is made of any suitable metallic (e.g., stainless steel, nitinol, tantalum, etc.), polymeric (e.g., polyethylene terephthalate, polyacetal, polylactic acid, polyethylene oxide-polybutylene terephthalate copolymer, etc.) or biodegradable material. The stent **300** is preferably metallic and configured in a mesh design, as shown in FIG. **3**. When used with the present invention, the stent **300** is placed over the expandable portion **120** of the catheter **110**.

The medical device **100** is thereafter delivered to a target location within the body. In this embodiment, the target location is situated within a body lumen. When the expandable portion **120** is expanded during the release of the drug agent from within the expandable portion **120** or the polymer coating **130**, the stent **300** is likewise expanded. After the drug agent has been released from the expandable portion **120** or the polymer coating **130**, the expandable portion **120** is compressed or deflated. The stent **300**, however, remains in its expanded state within the body lumen.

Referring to the embodiment of the invention illustrated in FIG. **4**, the expandable portion **120** of the catheter **110** is optionally covered by a protective sheath **210** while the medical device **100** is inserted into the body and positioned at a target location within a body lumen **200**. Such a sheath is particularly advantageous in the case of long arterial transit times (i.e., to position the catheter to the target location) or when the therapeutic agent to be delivered is highly toxic. As the expandable portion **120** is positioned at a target occluded site **220**, the protective sheath **210** is drawn back to expose the expandable portion **120** and thus to allow diffusion of the therapeutic agent into the target location **220**. Alternatively, the sheath **210** remains stationary while the catheter **110** moves the expandable portion **120** forward into the occluded region. The sheath **210** protects the agent and coating **130**, thus inhibiting premature release of the therapeutic agent.

In one embodiment, the medical device is a needle injection catheter rather than a balloon catheter. In this embodiment, the therapeutic agent is delivered to tissues atraumatically over a relatively short and clinically relevant time period, typically on the order of several seconds, by injecting a small volume (e.g., about 0.001 to about 1 ml) of a substantially saturated solution of therapeutic agent. Because the solution is substantially saturated, the concentration gradient of therapeutic agent resulting from injection drives the therapeutic agent deep into tissue by diffusion. Thus, in contrast to conventional local drug delivery techniques that make use of infusion pressure and volume to drive the drug deep into tissue, the method of the present invention achieves deep tissue penetration by a concentration driven mechanism. Consequently, the method of the present invention allows for the injection of therapeutic agent into tissues at low pressures, such as 1 atm or less, and with small volumes. One advantage of this embodiment over conventional techniques is that the low infusion pressure minimizes tissue damage, thus resulting in a potential increase in efficacy, transfection efficiency or the like.

Useful therapeutic applications to which the present invention can be applied include, without limitation, methods for treating, ameliorating, reducing and/or inhibiting any lumen or tissue injury, including those that result in denuding the interior wall of a lumen, namely its endothelial lining, including the lining of a blood vessel, urethra, lung, colon, urethra, biliary tree, esophagus, prostate, fallopian tubes, uterus, vascular graft, or the like. Such injuries result from disease, as in the case of atherosclerosis or urethal hyperplasia (strictures), and/or from mechanical injury from, for example, deployment of an endolumenal stent or a catheter-based device, including balloon angioplasty and related devices.

Vascular therapies that benefit using the methods disclosed herein include, without limitation, cardiomyopathies, cardiac and cerebral strokes, embolisms, aneurysms, atherosclerosis, and peripheral and cardiac ischemias. Delivery of genes encoding proteins competent to induce collateral blood vessel formation can be used to advantage in treating these disorders. Delivery of genes encoding proteins competent to interfere with neointimal (smooth muscle) cell proliferation also is particularly useful in treating restenosis.

Non-vascular therapies that benefit using the methods disclosed herein include urogential applications, including therapies for incontinence, kidney stones and the like. Here devices typically are implanted for a prescribed period of time and local delivery of genetic or chemical agents competent to induce an antibacterial, anti-inflammatory, or anti-encrustation effect are advantageous. In other applications, the delivery of anti-inflammatory agents, genetic or otherwise, is used to treat prostatitis, interstitial cystitis and other urogenital inflammatory disorders. Antiproliferative agents, genetic or otherwise, also can be used in endometriosis therapies. Still another application is in the delivery of anticancer agents, genetic or otherwise. The methods of the invention can be applied to therapies for bladder, prostate and uterine cancer. Similarly, delivery of agents to the interior of the lung to treat lung disorders, including cancers, cystic fibrosis and the like can be used to advantage.

The methods of the present invention can also be used to deliver diagnostic and/or imaging agents, including ultrasound contrasting agents such as perfluorocarbon. Other contrasting agents are well known to those skilled in the art. The contrasting agent is typically a microbubble encapsulated in a lipid, lipid-like or protein coat for catheter-based delivery. The microbubble further can have a tissue-targeting agent on its surface. Once delivered to the site of interest, the microbubble is burst or otherwise detected using ultrasound enhancement. The contrasting agent also can be combined with a therapeutic agent, genetic or otherwise, which then is delivered when the bubble is burst by ultrasound enhancement. Delivery to large surface areas such as lung and uterus interiors can benefit from this protocol.

Penetration enhancers are optionally used in any embodiment of the present invention. As is known in the art, penetration enhancers are substances or processes which facilitate the transport of solutes across biological membranes. When used in accordance with the present invention, penetration enhancers further increase the rate of penetration of therapeutic agents into tissues, thus allowing for more efficient drug transfer. Common classes of penetration enhancers include chelating agents such as EDTA, citric acid, salicylates, derivatives of collagen and diketones; surfactants such as SDS and polyoxyethylene-9-lauryl ether; non-surfactants such as cyclic ureas, 1-alkyl and 1-alkenylazacycloalkanone derivates; bile salts and derivates such as sodium deoxycholate, sodium, tauro-cholate, STDHF, and sodium glycodihydrofusidate; fatty acids and derivatives such as oleic acid, caprylic acid, capric acid, acylcarnitines, acylcholines, and mono and diglycerides; divalent and polyvalent cations; and enzymes such as elastase. Alternatively, a penetration enhancer used in conjunction with the present invention includes a process such as ultrasound, the application of an electric field, and/or other processes which increase the rate of penetration of therapeutic agents into tissues.

The invention is further described with reference to the following non-limiting examples.

EXAMPLES

All examples described herein were conducted for the in vivo delivery of an adenoviral trans-gene. The trans-gene used was recombinant nuclear specific β-galactosidase under the control of the cytomegalovirus promoter. Viral

titer was measured by standard plaque assay using 293 cells. Viral solutions were thawed on ice and diluted with saline to appropriate concentrations. The viral solutions were used immediately after dilution.

New Zealand white rabbits (3.5–4.0 kg) were anesthetized with ketamine (10 mg/kg) and acepromazine (0.2 mg/kg) following prededitation with xylazine (2 mg/kg). The bilateral external iliac arteries were used for all experiments. A 5 French ("Fr.") introducer sheath was positioned in the right common carotid artery under surgical exposure. An angioplasty catheter was introduced via the introducer sheath to the lower abdominal aorta under fluoroscopic guidance. Angiography of the iliac arteries was performed using 2 ml of non-ionic contrast media. Rabbit weights were monitored and kept within 3.5 to 4.0 kg to insure a balloon to artery ratio of about 1.2:1. Arteries were denuded of endothelium by conducting a triple inflation injury prior to delivery. Injury was conducted using a 2.0 cm, 3.0 mm diameter balloon catheter introduced with a 0.014 inch guidewire via the right common carotid artery into either the right or left external iliac artery. The catheter was inflated to pressure with 50% dilution of contrast media at 6 atm, three times for one minute per inflation. After treatment of one iliac artery, the contralateral iliac artery was treated with a new balloon catheter.

Replication-deficient adenoviral vector gene delivery was accomplished in vivo with the use of both infusion style local delivery catheters and hydrogel coated angioplasty catheters. The infusion based devices were used to deliver viral particles to the vessel wall by pressure driven convection combined with concentration driven diffusion. Transmural hydraulic pressure was created at the vessel wall and modulated using these devices by infusion the viral solution under a known applied pressure. Two infusion devices were used to modulate pressure at a constant delivery time: the Channeled balloon catheter (Boston Scientific Corporation, Natick, Mass.) was used for low to moderate infusion pressures and the Transport catheter (Boston Scientific Corporation, Natick, Mass.) was used for high pressure infusions. Concentration was modulated at a constant infusion pressure of approximately 0.1 atm. Additionally, hydrogel coated angioplasty balloons were used to deliver virus to the vessel wall by a purely concentration driven diffusive mechanism. The hydrogel coated angioplasty balloons were coated with a crosslinked polyacrylic acid polymer.

Example 1

Delivery with a Channeled Balloon Catheter

Replication deficient adenoviral vector gene delivery was accomplished in vivo with the use of a channeled balloon catheter 2.0 cm in length and 3.0 mm in diameter. The catheter was introduced with a 0.014 inch guidewire via the right common carotid artery into either the right or left external iliac artery. The balloon was inflated to a nominal pressure of about 6 atm, whereupon gene delivery was accomplished at an infusion pressure of about 0.1 or 3 atm. Either of 3 ml, 500 microliters ("μl"), or 200 μl of viral solution was infused through the infusion port of the catheter using a 1 ml or 5 ml syringe. Infusions of 3 ml were necessary to create higher infusion pressures. The solution was infused slowly over approximately 2 minutes while monitoring infusion pressure using an online pressure transducer. Balloons were deflated and removed after either 2 or 30 minutes had elapsed from the time of positioning the catheter at the target site.

Example 2

Delivery with a Transport Catheter

Viral solutions were infused locally at high pressure using the Transport catheter 2.0 cm in length and 3.0 mm in diameter. The catheter was introduced with a 0.014 inch guidewire via the right common carotid artery into either the right or left external iliac artery. The balloon was inflated to a nominal pressure of about 6 atm, whereupon gene delivery was accomplished at an infusion pressure of about 8 atm. Approximately 3 ml of viral solution was infused through the infusion port of the catheter using a 5 ml syringe. The solution was infused slowly over approximately 2 minutes while monitoring infusion pressure using an online pressure transducer. Balloons were deflated and removed after about 2 minutes.

Example 3

Delivery with a Hydrogel Coated Balloon Catheter

Virus was applied to the hydrogel coating of angioplasty balloons by slowly applying 25 μl of a 1.7×10^{11} pfu/ml adenoviral β-galactosidase stock solution (replication deficient adenovirus carrying the *E coli* β-galactosidase gene) onto the coating using a micro-pipette. A 2.0 cm long, 3.0 mm diameter loaded hydrogel coated balloon catheter was placed within a protective sheath and inflated to 2 atm. The entire assembly was advanced over a 0.014 inch guidewire via the right common carotid artery to the bifurcation leading to the external iliacs. The balloon was then deflated and quickly advanced further to either the right or left external iliac artery. Viral delivery was allowed to occur for either 2 or 30 min.

Comparison of Examples 1 to 3

Three days after transfection, iliac arteries were harvested immediately after perfusion with heparinized 0.9% saline solution via the lower abdominal aorta. The harvested vessels were washed with cold phosphate-buffered saline (PBS), fixed in 1% paraformaldehyde for 10 min, washed in PBS post-fixation. β-galactosidase activity was assessed by incubating arteries in X-GAL chromogen overnight at 37° C. After staining, vessels were rinsed in PBS and post-fixed in 1% paraformaldehyde.

Vessels were opened longitudinally and photographed through a dissecting microscope for gross assessment. The dark blue staining sites were considered transfected regions. The target-zone, usually at or near the center of the delivery site, was cross-sectioned and subsequently processed for histologic analysis. Specimens were embedded in paraffin sectioned into 5 μm sections and counter stained with hematoxylin and eosin. Slides were examined by light microscopy for expression of the LacZ transgene product, nuclear β-galactosidase, and were considered positive only when dark blue staining was observed. Transfection efficiency was determined by counting stained versus total medial nuclei in each arterial section.

Effect of Applied Pressure on Transfection

As shown in Table I, applied pressures of 3 and 8 atm did not significantly affect viral delivery from infusion-based devices. Transfection efficiency of a 3 ml viral solution was 2.30±0.64% when infused at approximately 3 atm and 1.05±0.21% when infused at an average pressure of 8 atm using Channeled and Transport catheters, respectively.

TABLE I

Influence of infusion volume and pressure on viral transfection efficiency.

Device	infused conc. (pfu/ml)	viral dose (pfu)	infusion volume (ml)	infusion pressure (atm)	% transduction
hydrogel	N/A	4.3×10^9	N/A	N/A	2.04 ± 0.75
channel	1.7×10^9	5.1×10^9	3	3	2.30 ± 0.64
transport	1.7×10^9	5.1×10^9	3	8	1.05 ± 0.21

p = NS for all combinations

A comparable level of gene transfection, 2.04±0.75%, was achieved at zero hydraulic pressure (no infusion volume) when the virus was delivered passively from a hydrogel coated balloon, providing an indication that molecular diffusion rather than convection is the predominant mechanism for viral transport in the vessel wall. Viral infusion volume and pressure were determined not to have a statistically significant effect (p=not significant ("NS")) on transfection efficiency under each condition tested in Table I (all data were compared by a one-way analysis of variants).

Effect of Infusion Volume on Cellularity

Cellularity was assessed in 5 micron histological cross-sections by counting the number of nuclei stained by hematoxylin and eosin. Cellularity is expressed as the number of nuclei per cross-section. The higher volume deliveries, and consequently higher pressure infusions, from Channeled and Transport balloon catheters resulted in a significant loss of cellularity in the treated segment, as shown in Table II.

TABLE II

Influence of delivery parameters on cellularity.

Device	infusion volume (ml)	infusion pressure (atm)	cellularity
none[1]	0	0	845 ± 34
hydrogel[2]	N/A	N/A	833 ± 17
channel[3]	0.2	0.1	800 ± 22
channel[4]	0.5	0.1	863 ± 24
channel[5]	3	3	592 ± 38
transport[6]	3	8	600 ± 34

*p < 0.05 for 1, 2, 3, 4 versus 5, 6

Sections from these arteries demonstrated a reduction in medial smooth muscle cell number as indicated by a loss of visible cell nuclei for vessels treated with 3 ml of viral solution. In contrast, infusion volumes of 500 μl and less did not exhibit any observable detrimental effects on vessel wall cellularity.

Effect of Concentration on Transfection

The effect of an applied concentration on in vivo gene delivery was examined by delivering 500 μl of viral solution at three concentrations, 1.7×10^{10}, 5.6×10^{10}, and 1.7×10^{11} pfu/ml, under an infusion pressure of 0.1 atm. Transfection increased by an order of magnitude from 1.8±0.4% to 17.8±3.2%, in direct proportion to the increase in viral concentration from 1.7×10^{13} to 1.7×10^{11} pfu/ml. Such transfection levels are considered high for in-vivo β-galactosidase because of the presence of endogenous inhibitors. Histological staining of these arteries demonstrated a greater number of stained blue cells deeper into the media at the higher concentration of delivered virus relative to the lower concentration. Previous studies (Schulick et al., "In vivo Gene Transfer into Injured Carotid Arteries. Optimization and Evaluation of Acute Toxicity," 91 Circulation 2407–14 (1995)) have demonstrated a toxic response in the vessel wall when 1×10^{10} pfu/ml of adenoviral β-galactosidase was delivered to rat carotid arteries. Here, the inventors have surprisingly shown that the channeled balloon catheter can be used to deliver viral solutions to rabbit iliac arteries at viral concentrations as high as 1.7×10^{11} pfu/ml without an adverse effect on cellularity and with no observable inflammatory response.

Effect of Delivery Time on Transfection

The effect of delivery time on gene transfection was examined using hydrogel coated balloons. The balloons were left in contact with the vessel wall for either 2 or 30 minutes. As shown in Table III, transfection efficiency was 1.57±0.05% and 2.04±75% for delivery at 30 minutes and 2 minutes, respectively. In a related set of experiments, 200 μl of viral solution infused through a channeled balloon catheter over 2 minutes followed by no incubation or a 30 minute incubation where the balloon was left inflated. Transfection was 2.53±0.44 and 2.00±0.52 for delivery with or without a 30 minute incubation, respectively.

TABLE III

Influence of delivery and incubation time on viral transfection efficiency.

Device	infused conc. (pfu/ml)	viral dose (pfu)	delivery time (min)	incubat. time (min)	% transduction
hydrogel[1]	N/A	4.3×10^9	2	0	2.04 ± 0.75
hydrogel[2]	N/A	4.3×10^9	30	0	1.57 ± 0.05
channel[3]	26×10^9	5.1×10^9	2	0	2.52 ± 0.44
channel[4]	26×10^9	5.1×10^9	2	30	2.00 ± 0.52

*p = NS for 1 vs. 2 and 3 vs. 4

Example 4

In accordance with an embodiment of the present invention, heparin is locally delivered with the use of an infusion style balloon, such as in a channeled balloon catheter. A substantially saturated solution of heparin, having a concentration of about 1 gram per 20 ml of water, is infused at a target location for about 2 minutes at a pressure of about 0.1 atm. Using this approach, relatively small volumes of approximately 1 ml may be infused to achieve a therapeutic result, in comparison to the relatively higher volumes and pressures used in conventional techniques.

Example 5

In accordance with an embodiment of the present invention, verapamil is locally delivered with the use of an infusion style balloon, such as in a channeled balloon catheter. A substantially saturated solution of verapamil hydrochloride, having a concentration of about 62 mg/ml (i.e., about 75% of the solubility limit of 82 mg/ml for verapamil hydrochloride in water), is infused at a target location for about 2 minutes at a pressure of about 0.1 atm. Using this approach, relatively small volumes of approximately 1 ml may be infused to achieve a therapeutic result, in comparison to the relatively higher volumes and pressures used in conventional techniques.

Summary of Examples 1–5

By way of the present invention, a 2-minute clinically relevant delivery time was shown to be effective in achieving high levels of gene transfection in vivo. While prior studies have used delivery times greater than 20 minutes or an additional 30 minute incubation period post delivery from

an infusion device such as a channel balloon catheter, the present inventors have shown that a 2 minute delivery time is at least or more effective than 30 minute delivery times. Since molecular diffusion is time-dependent, longer delivery times may have a positive effect under different conditions such as higher viral doses. In addition, a 30 minute incubation period post viral delivery from an infusion device, i.e. channel balloon catheter, was shown not to have a significant effect on gene expression. Thus, once the artery is reperfused and the concentration gradient is reversed, the virus does not back diffuse into the lumen. As the inventors have shown, long delivery times and extended incubation periods are not necessary for effective gene transfer once conditions have been optimized for a particular delivery device.

Example 6

Delivery with a Needle Injection Catheter

Recombinant replication deficient adenoviral particles encoding the gene for β galactosidase were injected into porcine myocardia using a needle injection catheter. A volume of 100 μl of viral solution was injected at a concentration of 1×10^9 pfu/ml and the results compared to those obtained using a 100 kl dose injection at 1×10^{10} pfu/ml. Greater penetration of the virus was observed with the higher concentration injection, thus demonstrating greater diffusion of the virus due to the corresponding higher concentration gradient. Moreover, the higher concentration injection demonstrated greater transfection when compared to 250 μl injections at lower concentrations of 1×10^9 pfu/ml, thus demonstrating that high volumes are not necessary to achieve high degrees of transfection.

The inventors have demonstrated that viral particles penetrate arterial tissue in a manner analogous with a molecular diffusion mechanism. Consistent with this finding, the inventors have determined that concentration of therapeutic agent is the critical parameter for transport, and thus gene expression or therapeutic effect, in a vessel wall. The present invention is used to achieve significant transfection levels or therapeutic agent levels at a local site by delivering a small volume of concentrated therapeutic agent solution through a local delivery catheter at low pressure. Conversely, the inventors have determined that variations in applied pressure, which drives convective transport, does not significantly affect gene expression or drug delivery and/or uptake. Moreover, the inventors have found that gene expression occurs when a viral solution is delivered in a clinically relevant time frame of 2 minutes, thus indicating that longer times are not necessary to achieve efficient gene transfer.

What is claimed is:

1. A method of site-specifically delivering a therapeutic agent to a target location within a body cavity, vasculature, or tissue of a mammal, comprising the steps of:

providing a catheter having a substantially saturated solution of therapeutic agent associated therewith, said therapeutic agent selected from the group consisting of pharmaceutically active molecules, proteins, and nucleic acids encoding an angiogenic factor,

introducing said catheter into the body cavity, vasculature, or tissue;

wherein a volume of said solution of therapeutic agent is released from said catheter at the target location at a pressure not more than about 0.1 atmospheres.

2. The method of claim 1, wherein said catheter is a channeled balloon catheter.

3. The method of claim 1, wherein said catheter is a transport catheter.

4. The method of claim 1, wherein said catheter is an infusion sleeve catheter.

5. The method of claim 1, wherein said catheter is balloon catheter having an expandable portion.

6. The method of claim 5, further comprising the steps of:

coating said expandable portion with a polymer coating; and

incorporating said therapeutic agent into said polymer coating.

7. The method of claim 6, wherein said coating comprises a polymer selected from the group consisting of polycarboxylic acids, cellulosic polymers, gelatin, polyvinylpyrolidone, maleic anhydnde polymers, polyamides, polyvinyl alcohols, polyethylene oxides, glycosamnoglycans, polysacchaxides, polyesters, polyuretbanes, silicones, polyorthoesters, polyanhydrides, polycarbonates, polypropylenes, polylactic acids, polyglycolic acids, polycaprolactones, polybydroxybutyrate valerates, polyacrylamides, polyethers, polyurethane dispersions, acrylic latex dispersions, polyacrylic acid, and mixtures and co-polymers thereof.

8. The method of claim 5, further comprising the steps of:

placing a sheath over said expandable portion before said step of positioning said catheter to said target location; and

removing said expandable portion from said sheath before said step of releasing said solution of therapeutic agent from said catheter.

9. The method of claim 1, wherein said catheter comprises a needle.

10. The method of claim 9, wherein said catheter is a needle injection catheter.

11. The method of claim 9, wherein said needle is a hypodermic needle.

12. A method of site-specifically delivering a therapeutic agent selected from the group consisting of therapeutically active molecules, protein and nucleic acids encoding an angiogenic factor to a target location within a body cavity or vasculature of a mammal, comprising the steps of:

providing a catheter having a substantially saturated solution of therapeutic agent incorporated therein, said solution comprising a physiologically acceptable solvent and said therapeutic agent and wherein the concentration of said therapeutic agent in said solution is at least about 75% of the limit of solubility of said therapeutic agent in said solvent,

introducing said catheter into the body cavity or vasculature;

positioning said catheter to said target location;

wherein said solution of therapeutic agent is released from said catheter at a pressure not more than about 0.1 atmospheres.

13. The method of claim 12, wherein said catheter is a channeled balloon catheter.

14. The method of claim 12, wherein said catheter is a transport catheter.

15. The method of claim 12, wherein said catheter is an infusion sleeve catheter.

16. The method of claim 12, wherein said catheter is a balloon catheter having an expandable portion.

17. The method of claim 16, further comprising the steps of,

coating said expandable portion with a polymer coating; and

incorporating said therapeutic agent into said polymer coating.

18. The method of claim 17, wherein said coating comprises a polymer selected from the group consisting of polycarboxylic acids, cellulosic polymers, gelatin, polyvinylpyrrolidone, maleic anhydride polymers, polyamides, polyvinyl alcohols, polyethylene oxides, glycosaminoglycans, polysaccharides, polyesters, polyurethanes, silicones, polyorthoesters, polyanhydrides, polycarbonates, polypropylenes, polylactic acids, polyglycolic acids, polycaprolactones, polyhydroxybutyrate valerates, polyacrylamides, polyethers, polyurethane dispersions, acrylic latex dispersions, polyacrylir acid, and mixtures and co-polymers thereof.

19. The method of claim 17, further comprising the steps of

placing a sheath over said expandable portion before said step of positioning said catheter to said target location; and

removing said expandable portion from said sheath before said step of releasing said solution of therapeutic agent from said catheter.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,369,039 B1
DATED : April 9, 2002
INVENTOR(S) : Palasis et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 4,
Line 4, "mean" should read -- means --.

Column 5,
Line 29, "anticodies" should read -- antibodies --; and
Line 42, "vascoactive" should read -- vasoactive --.

Column 6,
Line 1, "enotheial" should read -- endothelial --.

Column 9,
Line 34, "infusion the" should read -- infusion of the --.

Column 11,
Line 58, "1.7x1013" should read -- 1.7x1010 --.

Column 12,
Line 1, "1x1010" should read -- 1x1011 --.

Column 13,
Line 23, "100 kl" should read -- 100 µl --.

Column 14,
Line 13, "anhydnde" should read -- anhydride --;
Line 15, "glycosamnoglycans" should read -- glycosaminoglycans --;
Line 15, "polysacchaxides" should read -- polysaccharides --; and
Line 18, "polybydroxybutyrate" should read -- polyhydroxybutyrate --;

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,369,039 B1
DATED : April 9, 2002
INVENTOR(S) : Palasis et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 15,
Line 11, "polyacrylir" should read -- polyacrylic --;

Signed and Sealed this

Twenty-eighth Day of January, 2003

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/542,935	04/04/2000	Maria Palasis	02844/56301	5876

26646 7590 08/15/2006

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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 08/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/542,935	PALASIS, MARIA	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *60,62 and 65-91* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *60,62,65-91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ *Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)* Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 60, 62, and 65-91 are pending.

Applicant's traversal filed on 6/6/06 is acknowledged and considered by the examiner.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Instant claims 60, 62, and 65-91 are unsupported under 35 U.S.C. 112, first paragraph, as failing to comply with the 112 first paragraph written description.

The original specification (09/204,254 filed 12/3/98, now US 6,369,039) did not disclose making and using a medical device comprising a biocompatible structure carrying a genetic material, said biocompatible structure comprising an angiogenic agent selected from acidic fibroblast growth factor, basic fibroblast growth factor, vascular growth factor, epidermal growth factor, transforming growth factor alpha and beta, platelet-derived growth factor, and platelet-derived growth factor. However, the list set forth in the new claims does not include all of the products listed in the specification that are considered angiogenic agents (e.g., hif-1). The

specification does not disclose the subgenus set in the new claims and claims dependent therefrom. Thus, nothing in the specification would lead one to the particular combination set forth in the amended and claims dependent therefrom and new claims. "It is not sufficient for purposes of the written description requirement of Section 112 that the disclosure, when combined with the knowledge in the art, would lead one to speculate as to modifications that the inventor might have envisioned, but failed to disclose." *Lockwood v. American Airlines Inc.*, 41 USPQ2d 1961, 1966 (CAFC 1997).

Thus, the instant claims 60, 62, and 65-91 in the application do not enjoy priority to application '254 filed on 12/3/98.

Applicant's arguments filed 6/6/06 have been fully considered but they are not persuasive.

In response to applicant's argument that support for claim 71 can be found on col 5. line 66 of the 6,369,039 patent (US 09/204,254), the argument is not found persuasive because while it is acknowledged that acidic or basic fibroblast growth factor is listed in col. 5, line 66, the limitation is directed to either acidic or basic fibroblast growth factor or DNA encoding acidic or basic fibroblast growth factor. The limitation does not embrace using an acidic or basic fibroblast growth factor and DNA encoding either factor. There is nothing in the specification of '039 to lead the skilled artisan to using both in the medical device.

In response to applicant's argument that support for claim 72 can be found on col 5. lines 66-67 of the '039 patent, the argument is not found persuasive because while it is acknowledged that vascular endothelial growth factor is listed in col. 5, lines 66-67, the limitation is directed to either vascular endothelial growth factor (VEGF) or DNA encoding VEGF. The limitation does

not embrace using a VEGF growth factor and DNA encoding VEGF. There is nothing in the specification of '039 to lead the skilled artisan to using both in the medical device.

In response to applicant's argument that support for claim 73 can be found on col. 6. line 2 of the '039 patent, the argument is not found persuasive because while it is acknowledged that platelet derived growth factor (PDGF) is listed in col. 6, line 2, the limitation is directed to PDGF or DNA encoding PDGF. The limitation does not embrace using a PDGF and nucleic acid encoding PDGF. There is nothing in the specification of '039 to lead the skilled artisan to using both in the medical device.

In response to applicant's argument that support for claim 74 can be found on col. 6. line 1 of the '039 patent, the argument is not found persuasive because while it is acknowledged that platelet derived endothelial growth factor (PDEGF) is listed in col. 6, line 1, the limitation is directed to PDEGF or DNA encoding PDEGF. The limitation does not embrace using a PDEGF and nucleic acid encoding PDEGF. There is nothing in the specification of '039 to lead the skilled artisan to using both in the medical device.

In response to applicant's argument that support for claim 75 can be found on col. 5. lines 66-67 of the '039 patent, the argument is not found persuasive because while it is acknowledged that epidermal growth factor (EGF) is listed in col. 5, lines 66-67, the limitation is directed to EGF or DNA encoding PDEGF. The limitation does not embrace using an EGF and nucleic acid encoding EGF. There is nothing in the specification of '039 to lead the skilled artisan to using both in the medical device.

In response to applicant's argument that support for claim 76 can be found on col. 5. line 67 to col. 6, line 1 of the '039 patent, the argument is not found persuasive because while it is

acknowledged that transforming growth factor alpha or beta (TGF-alpha or TGF-beta) is listed in col. 5, lines 67 to col. 6, line 1, the limitation is directed to TGF-alpha or beta or DNA encoding TGF-alpha or beta. The limitation does not embrace using TGF-alpha or beta and nucleic acid encoding TGF-alpha or beta. There is nothing in the specification of '039 to lead the skilled artisan to using both in the medical device.

In response to applicant's argument that none of the case law cited by applicant is appropriate because there is exact support in the specification for the recited angiogenic agents, the argument is not found persuasive because there is no exact support in the specification of '254 for the claimed method. Application '254 does not specifically recite making and/or using a medical device comprising an angiogenic agent (angiogenic protein) and a vector comprising a nucleic acid encoding an angiogenic agent. Furthermore, the applicant did not disclose using a list of angiogenic agents excluding hif-1, NOS and any other angiogenic agent listed in the instant specification from the subgenus listed in the instant claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 60, 62, and 65-91 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New Matter rejection:

Amended claims 60 and 62 and claims 65-91 filed on 2/1/06/04 introduce new subject matter into the application.

With respect to the limitation 'a therapeutic agent, wherein said therapeutic agent is an angiogenic agent and a vector containing a polynucleotide that established a gene expression sufficient to produce a therapeutically sufficient amount of one or more products encoded by said polynucleotide, wherein said polynucleotide encodes a polypeptide or protein, wherein said polypeptide or protein is an angiogenic agent' in amended claims 60 and 62 and claims dependent therefrom, the original specification did not disclose the limitation. The asserted support cited for the limitation in the claims does not provide support for the limitation. Page 18, lines 18-22 is directed to the angiogenic agents listed in the dependent claims. However, the specification discloses that either the first or the second polynucleotide or both encode the angiogenic agents. There is no disclosure in the specification of an angiogenic agent and a polynucleotide encoding an angiogenic agent. In addition, page 17, line 20 through page 18, line 16 lists several angiogenic agents that are excluded from the instant claims. The instant specification does not disclose the subgenus set forth in the new claims. It is apparent that the applicants at the time the invention was made did not intend or contemplate making and/or using the medical device set forth in the amended claims and newly added claims as part of the disclosure of their invention. There is no evidence in the specification that the applicants were

possession of the medical device as set forth in the newly filed claims and amended claims, as it is now claimed, at the time the application was filed.

Applicant's arguments filed 6/6/1/06 have been fully considered but they are not persuasive for the reasons set forth under priority.

In response to applicant's argument that original claim 26 provide support for the instant claims because claim 26 described a first therapeutic agent that is a genetic material and a second therapeutic agent that is a non-genetic material, the argument is not found persuasive for the reasons of record and was already in the previous office action. See page 6 of office action mailed on 3/6/06.

In response to applicant's argument that original claim 26 provide support for the instant claims because claim 33 described both the first therapeutic agent and second therapeutic agent cause the production of an angiogenic agent, the argument is not found persuasive for the reasons of record and was already in the previous office action. See page 6 of office action mailed on 3/6/06.

Applicant's argues that the Written Description Guidelines issued by the USPTO clearly state that "there is no *in haec verba* requirement" to satisfy written description and that newly added claim limitations can be supported through "express, implicit, or inherent disclosure." See Guidelines for the Examination of Patent Application Under 35 USC 112 para1, "Written Description" Requirement (Fed. Reg. Vol. 66, No. 4, January 5, 2001, page 13.

Applicant's argument is not found persuasive because while it is acknowledged that there is not implicit requirement to satisfy written description, there is no guidance in the specification for one of ordinary skill in the art to make and use a medical device comprising a nucleic acid

encoding an angiogenic agent and an angiogenic agent. When an explicit limitation in a claim "is not present in the written description whose benefit is sought it must be shown that a person of ordinary skill in the art would have understood, at the time the patent application was filed, that the description requires the limitation." Hyatt v. Boone, 146 F.3d 1348, 1353, 47 USPQ2d 1128, 1131 (Fed. Cir. 1998).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 60, 62, 65, 67, 68, 69, 71, 72, 73, 75, 77-80, 82-84, 86, 87, 88, 90, and 91 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Roth (US 5,879,713) taken with Crystal et al. (US 5,869,037). Roth teaches delivering to a vascular system of an animal a biodegradable, biocompatible polymeric microparticles comprising biologically active molecules selected from the group consisting of growth factors, cytokines, angiogenesis factors,

immunosuppressant molecules, peptide fragments thereof and nucleic acid constructs capable of synthesizing these compounds, wherein restenosis has occurred following balloon angioplasty (abstract and columns 10 and 16-18). Roth teaches the limitation in instant claims 78 and 79 (columns 10 and 16-18). The growth factors can be VEGF, bFGF, and PDGF and DNA encoding them (column 10). The biologically active molecules, which are immobilized on the polymeric microparticles can include proteins, nucleic acid molecules, carbohydrates, lipids and combinations thereof (column 9). Roth teaches the limitation in instant claim 67 (columns 3-4). Roth teaches the limitation in instant claim 68 (column 11). Roth teaches the limitation in instant claims 69 and 84 (column 11). However, Roth does not specifically teach using a nucleic acid encoding an angiogenic agent and an angiogenic agent in the microparticles.

However, at the time the invention was made, Crystal teaches composition comprising a viral vector comprising a nucleic acid encoding a VEGF polypeptide (column 11). Crystal teaches that the composition can be formulated into preparations in solids (column 11). Crystal further teaches that the vector can be delivered with other means of stimulating angiogenesis such as treatment with other angiogenic growth factors (column 11). One of ordinary skill in the art understands that adenovirus provides an efficient means for transferring biological materials to target cells (columns 1 and 2).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Roth taken with Crystal, namely to produce a medical device comprising a polymeric coating comprising a vector comprising a polynucleotide encoding an angiogenic agent and an angiogenic agent. One of ordinary skill in the art would have been motivated to combine the teaching to enhance the circulation where there has been

vascular occlusion. See also In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Roth taken with Crystal, namely to use the medical device to treat restenosis in a patient. One of ordinary skill in the art would have been motivated to combine the teaching to deliver the agents in a controlled and sustained manner as exemplified by Roth (column 2).

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Roth taken with Crystal, namely to use an adenovirus in the medical device for treating a patient with restenosis. One of ordinary skill in the art would have been motivated to combine the teaching to improve the delivery of the nucleic acid to the cells of interest as exemplified by Crystal (columns 1 and 2).

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 6/6/06 have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). This is the case here. The prior art teaches using a nucleic acid encoding an angiogenic agent (see Crystal) and an angiogenic

polypeptide (See Roth). See In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Claims 60, 62, 65, 66, 80, and 81 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Roth et al. taken with Crystal et al. as applied to claims 60, 62, 65, 67, 68, 69, 71, 72, 73, 75, 77-80, 82-84, 86, 87, 88, 90, and 91 above, in further view of Branellec et al. (US Patent No. 5,851,521, cited on a previous PTO-892).

However, Roth and Crystal do not specifically making and using a viral vector (AAV) to deliver the nucleic acid.

However, at the time the invention was made, replication defective AAV viral vectors were well known to one of ordinary skill in the art for delivering nucleic acid to cells using a catheter and using micro-particles (e.g. polylactide) to deliver said nucleic acid (column 9, line 60-column, line 67). Branellec teaches using AAV vectors comprising a protein in a method inhibiting restenosis in a mammal (abstract and column 7, lines 55-65). AAV vectors are able to infect a wide spectrum of cells without inducing any effect on cellular growth, morphology, or differentiation and they do not appear to be involved in human pathologies.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Roth taken with Crystal in further view of Branellec, namely to produce the microparticle comprising a replication defective AAV vector. One of ordinary skill in the art would have been motivated to combine the teaching and make the microparticle comprising a replication defective AAV vector because AAV vectors are well

known to one of ordinary skill in the art to be non-pathogenic in vivo and infect a wide spectrum of cells without inducing any effect on cellular growth, morphology, or differentiation.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Roth taken with Crystal in further view of Branellec, namely to use a replication defective AAV vector in the microparticle for delivering a genetic material to a mammal. One of ordinary skill in the art would have been motivated to combine the teaching and use the replication defective AAV in the method because AAV vectors are non-pathogenic in mammals and are well known to one of ordinary skill in the art for delivering a nucleic acid to a mammal with restenosis as exemplified by Branellec (column 7).

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 6/6/06 have been fully considered but they are not persuasive because the argument was already addressed in the first 103 rejection.

Claims 60, 62, 69, 70, 84, and 85 remain rejected under 35 U.S.C. 103(a) as being unpatentable Roth et al. taken with Crystal et al. as applied to claims 60, 62, 65, 67, 68, 69, 71, 72, 73, 75, 77-80, 82-84, 86, 87, 88, 90, and 91 above, and further in view of with Donovan et al. (US 5,833,651, cited on a previous PTO-892).

However, Roth and Crystal do not specifically making and using a metallic stent to deliver the vector and the angiogenic agent.

However, at the time the invention was made, Donovan teaches that metallic stents are well known to one of ordinary skill in the art for delivering microparticles to an area of a mammal (columns 5-6).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Roth taken with Crystal in further view of Donovan, to make a metallic stent comprising the microparticle. One of ordinary skill in the art would have been motivated to combine the teaching, as a matter of designer's choice, and make a metallic stent comprising the microparticle because metallic stents are well known to one of ordinary skill in the art for delivering a microparticle to an area of a mammal as exemplified by Donovan (columns 5-6).

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Roth taken with Crystal in further view of Donovan, namely to use a metallic stent for delivering the microparticle to an area of a mammal. One of ordinary skill in the art, as a matter of designer's choice, would have been motivated to combine the teaching and use a metallic stent in the method because metallic stents are well known to one of ordinary skill in the art for sustainable delivery of microparticles to an area of a mammal as exemplified by Donovan (columns 5-6).

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments with respect to claims 60 and 62 have been considered but are moot in view of the new ground(s) of rejection.

Applicant's arguments filed 6/6/06 have been fully considered but they are not persuasive because the argument was already addressed in the first 103 rejection.

Claims 60, 62, 74, 76, and 89 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Roth taken with Crystal as applied to claims 60, 62, 65, 67, 68, 69, 71, 72, 73, 75, 77-80, 82-84, 86, 87, 88, 90, and 91 above, and further in view of Isner (US 5,652,225).

However, Roth taken with Crystal do not specifically teach using PEGF and TGF alpha or TGF beta.

However, at the time the invention was made, PEGF, TGF-alpha and TGF beta were known to one of ordinary skill in the art as angiogenic proteins as taught by Isner. See column 3.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Roth and Crystal in further view of Isner, namely to use PEGF in the method. One of ordinary skill in the art would have been motivated to combine the teaching because PEGF is a growth factor that can be used to induce angiogenesis in a patient.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Roth and Crystal in further view of Isner, namely to use either TGF alpha or TGF beta in the method. One of ordinary skill in the art would have been motivated to combine the teaching because TGF alpha and TGF beta are growth factors that can be used to induce angiogenesis in a patient.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 6/6/06 have been fully considered but they are not persuasive because the argument was already addressed in the first 103 rejection.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, SPE – Art Unit 1635, can be reached at (571) 272-4517.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of

such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center number is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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Brian Whiteman

BRIAN WHITEMAN
PATENT EXAMINER

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE			
AMENDMENT TRANSMITTAL LETTER		Docket Number: **12013/56301**	
Application Number 09/542,935	Filing Date April 4, 2000	Examiner B. A. Whiteman	Art Unit 1635
Invention Title **INSERTABLE OR IMPLANTABLE MEDICAL DEVICES SUITABLE FOR GENE THERAPY REGIMENS**		**Inventors** **Maria PALASIS**	

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on

Date: 11/10/06

Signature: Lynne Fitch

Sir:

1. Transmitted herewith for filing is an Amendment.

2. The filing fee has been calculated after entry of the accompanying Amendment as shown below:

	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT NUMBER EXTRA	RATE ($)	FEE ($)
TOTAL CLAIMS	29	minus	91	0	50.00	0.00
INDEPENDENT CLAIMS	2	minus	3	0	200.00	0.00
MULTIPLE DEPENDENT CLAIM ADDED					360.00	0.00
					TOTAL	0.00
				SMALL ENTITY TOTAL		

3. No additional claim fees are believed due. The Commissioner is hereby authorized to charge payment of the following fees associated with this communication or to credit any overpayment to the deposit account of **Kenyon & Kenyon LLP**, deposit account number **11-0600**:

   A. Any additional filing fees required under 37 C.F.R. § 1.16;

   B. Any additional patent application processing fees under 37 C.F.R. § 1.17;

   C. Any additional patent issue fees under 37 C.F.R. § 1.18;

   D. Any additional document supply fees under 37 C.F.R. § 1.19;

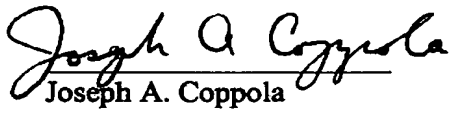
   E. Any additional post-patent processing fees under 37 C.F.R. § 1.20; or

   F. Any additional miscellaneous fees under 37 C.F.R. § 1.21.

4. A copy of this letter is enclosed.

Respectfully submitted,

Date: November 10, 2006



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[Attorney Docket: 12013/56301]

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor :	Maria PALASIS	Art Unit :	1635
Serial No.:	09/542,935	Examiner :	B. A. Whiteman
Filing Date:	April 4, 2000		
For:	Insertable or Implantable Medical Devices Suitable for Gene Therapy Regimens		

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Alexandria, VA 22313-1450

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Date: 11/10/06

Signature: Lynne Fetch

AMENDMENT UNDER 37 C.F.R. §1.116

SIR:

In response to the Office Action dated August 15, 2006 containing a Final Rejection, please consider the following remarks intended to simplify the issues for appeal.

REMARKS

Claims 60, 62, and 65-91 are pending.

Priority

The Office Action stated that the claims are not entitled to the priority date of U.S. Patent Application Serial No. 09/204,254 (now U.S. Patent No. 6,369,039; hereinafter "the '039 patent"). The Office Action provided two reasons for this conclusion:

(1) The '039 patent does not contain a written description of the subgenus of angiogenic agents supposedly set forth in the claims. See the Office Action, paragraph bridging pages 2-3:

> However, the list set forth in the new claims does not include all of the products listed in the specification [of the ''039 patent] that are considered angiogenic agents (e.g., hif-1). The specification [of the ''039 patent] does not disclose the subgenus set [sic, forth?] in the new claims and claims dependent therefrom. Thus, nothing in the specification [of the '039 patent] would lead one to the particular combination set forth in the amended and claims dependent therefrom and new claims [sic].

The Applicant wishes to point out that the present claims do not contain a list of angiogenic agents that is a subgenus of any lists disclosed in the '039 patent. The Applicant believes that the present claims are as shown in the Appendix to this paper. Certain of the present dependent claims recite particular angiogenic agents but no lists of angiogenic agents appear in the present claims. Accordingly, it does not seem that the Office Action's comments are applicable to the present claims.

(2) All the present claims recite a combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent. In its discussion of the dependent claims, the Office Action argued that there is no disclosure in the '039 patent of the use of <u>both</u> an

angiogenic agent and a polynucleotide encoding an angiogenic agent. Instead, according to the Office Action, the '039 patent only discloses the use of either an angiogenic agent or a polynucleotide encoding an angiogenic agent. See, e.g., the Office Action, page 3, second paragraph from bottom:

> [W]hile it is acknowledged that acidic or basic fibroblast growth factor or DNA encoding acidic or basic fibroblast growth factor is listed in col. 5, line 66 [of the '039 patent], the limitation is directed to either acidic or basic fibroblast growth factor or DNA encoding acidic or basic fibroblast growth factor. The limitation does not embrace using an acidic or basic fibroblast growth factor and DNA encoding either factor. There is nothing in the specification of '039 to lead the skilled artisan to using both in the medical device.

The Applicant respectfully disagrees. The combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent is disclosed in the paragraph at col. 5, l. 49 to col. 6, l. 22 of the '039 patent. In this passage, the '039 patent first makes clear that the polymeric coating of the devices described therein can include polynucleotides encoding therapeutic agents ("Polynucleotide sequences useful in practice of the invention include DNA or RNA sequences having a therapeutic effect after being taken up by a cell;" col. 5, ll. 49-51). The '039 patent then states that, **in addition to** the polynucleotides, the polymeric coating may contain polypeptides and proteins ("In addition, the polypeptides or proteins that can be incorporated into the polymeric coating ... ;" col. 5, ll. 62-64). This is followed by a list of suitable therapeutic agents, including the angiogenic agents that are recited in the present claims.

The combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent is also disclosed in the paragraph at col. 4, l. 64 to col. 5, l. 48. This paragraph teaches that polynucleotides (col. 4, l. 67, to col. 5, l. 4) and angiogenic agents (col. 5, ll. 15-16) can be in the polymeric coating. It is then stated that combinations of polynucleotides and

angiogenic agents can be in the coating ("and combinations thereof;" col. 5, l. 44). That the polynucleotides may encode angiogenic agents is taught at col. 5, ll. 62-65.

The present claims are therefore entitled to the priority date of U.S. Patent Application Serial No. 09/204,254 (now U.S. Patent No. 6,369,039).

Accordingly, it is respectfully requested that the denial of priority be reconsidered.

The rejection under 35 U.S.C. §112

The claims were rejected for failure to comply with the written description requirement because the present specification supposedly does not disclose the use of both an angiogenic agent and a polynucleotide encoding an angiogenic agent. See the Office Action, page 6, last paragraph:

> [T]he specification discloses that either the first or the second polynucleotide or both encode the angiogenic agents. There is no disclosure in the specification of an angiogenic agent and a polynucleotide encoding an angiogenic agent.

The Applicant respectfully traverses this rejection. The present claims have written description support in the present application. In particular, the present application discloses the use of an angiogenic agent and a polynucleotide encoding an angiogenic agent. This can be readily seen by examining the following table, which demonstrates that the language of claim 60 closely tracks the language found in the Summary of the Invention of the present application (page 5, lines 3-11). This comparison demonstrates the presence of the

combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent in both claim 60 and the Summary of the Invention.

A medical device comprising:	... a medical device having
a biocompatible structure comprising a polymeric coating that coats at least a portion of said structure, said polymeric coating comprising:	a biocompatible structure carrying a genetic material. The biocompatible structure comprises a biocompatible polymeric coating that coats at least a portion of the structure and carries a genetic material. The genetic material comprises:
(A) a therapeutic agent, wherein said therapeutic agent is an angiogenic agent, and	(a) a second[1] therapeutic agent comprising at least one of (i) a second polynucleotide carried by a carrier; (ii) a protein; (iii) **a non-genetic therapeutic agent**, or (iv) cells [emphasis added]
(B) a vector containing a polynucleotide that establishes a gene expression sufficient to produce a therapeutically sufficient amount of one or more products encoded by said polynucleotide, wherein said polynucleotide encodes a polypeptide or protein, wherein said polypeptide or protein is an angiogenic agent.	(b) a first therapeutic agent comprising a vector containing a first polynucleotide that establishes a gene expression sufficient to produce a therapeutically sufficient amount of one or more products encoded by said first polynucleotide

The primary difference between claim 60 and the disclosure at page 5, lines 3-11 is that claim 60 limits the first therapeutic agent at page 5, line 6 to a polynucleotide encoding an angiogenic agent and claim 60 limits the second therapeutic agent (i.e., the non-genetic therapeutic agent at page 5, line 10) to an angiogenic agent. Support for these limitations

[1] For ease of comparison to claim 60, (a) and (b) from the disclosure at page 5, lines 3-11 have been transposed.

with respect to angiogenic agents is found in those portions of the present application that teach that both the therapeutic agents may be angiogenic agents. See, e.g., page 18, line 1.

See also original claim 33, which states that "said first therapeutic agent, said second therapeutic agent, **or both**" [emphasis added] can be angiogenic agents. Original claim 33 depends from original claim 26, which, in one of its embodiments, is directed to the combination of a polynucleotide and a non-genetic therapeutic agent. Thus, original claim 33 teaches that the Applicant contemplated the combination of a polynucleotide and a non-genetic therapeutic agent where both the polynucleotide encodes an angiogenic agent and the non-genetic therapeutic agent is an angiogenic agent.

One or ordinary skill in the art is again directed to this combination at page 22, line 21 to page 23, line 6, where a preferred embodiment of the invention is disclosed as:

> A preferred embodiment of this invention is to provide treatment of vascular thrombosis and angioplasty restenosis, particularly coronary vascular thrombosis, and angioplasty restenosis, thereby to decrease incidence of vessel rethrombosis and restenosis, unstable angina, myocardial infarction and sudden death. The medical device and method of this invention can be used to treat patients having severe complications resulting from thrombus. Specific examples include patients with acute myocardial infarction (AMI) and patients that have failed PTCA (percutaneous transluminal coronary angioplasty) and have abrupt thrombotic closure of the targeted artery.

From this passage, one of ordinary skill in the art would recognize that one aspect of the invention is designed to increase blood flow and thereby oxygen delivery to tissues, particularly to tissues sensitive to disruptions in cardiovascular perfusion. One of ordinary skill in the art would recognize that this can be accomplished through a local increase of blood flow by the development and expansion of blood vessels in an area of potential stenosis or thrombotic blockage, i.e., by angiogenesis. Thus, this passage directs one of ordinary skill in the art to the choice of "angiogenic agents" as the therapeutic agents of the invention.

Furthermore, in Example 7 on pages 28-29, the specification discloses an embodiment in which both therapeutic agents are "angiogenic agents." This example discloses a medical device comprising polynucleotides encoding VEGF protein and FAS Ligand protein.

The specification indicates that VEGF protein is a "promoter of endothelialization" (Example 7, page 29, line 3), i.e., an angiogenic agent. Moreover, it is well known in the art that VEGF protein is known to play a critical and central role in angiogenesis. FAS Ligand is also well-known to promote angiogenesis.

Thus, Example 7 clearly directs the skilled person to the concept of practicing the invention wherein **both** therapeutic agents are angiogenic agents. Although Example 7 describes the use of two genetic therapeutic agents rather than the presently claimed combination of a genetic therapeutic agent and a non-genetic therapeutic agent, the concept of using both a genetic therapeutic agent and a non-genetic therapeutic agent is clearly described elsewhere (see discussion above) and would have been understood as being suitable for combination with the concept of Example 7 that both therapeutic agents can be angiogenic agents.

Other portions of the present application also provide written description support for the recited combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent.

The combination of a therapeutic agent comprising genetic material, e.g., a polynucleotide, with a non-genetic therapeutic agent is clearly disclosed at page 17, lines 6-8:

> The first therapeutic agent of this invention comprises genetic materials whereas the second therapeutic agent of the invention may comprise either genetic or non-genetic materials.

The reference to the "first therapeutic agent" in this passage would be understood in light of prior disclosures in the specification which teach that the "first therapeutic agent" is preferably a polynucleotide. See, e.g., page 5, lines 6-7 ("a first therapeutic agent comprising ... a first polynucleotide ..."); page 6, line 9 ("a first therapeutic agent comprising ... a first polynucleotide ..."). Thus, the passage at page 17, lines 6-8 quoted above would be understood as teaching the combination of a first therapeutic agent that is a polynucleotide with a non-genetic therapeutic agent.

In the second paragraph after the above disclosure at page 17, lines 6-8 of the combination of a first therapeutic agent that is a polynucleotide with a non-genetic therapeutic agent, there is a disclosure that both therapeutic agents can be angiogenic agents (page 18, line 1). The disclosures at page 17, lines 6-8 and page 18, line 1 would be reinforced by original claim 33; page 22, line 21 to page 23, line 6; and Example 7, all of which, as explained above, teach that the Applicant contemplated the combination of a polynucleotide and a non-genetic therapeutic agent where the polynucleotide encodes an angiogenic agent and the non-genetic therapeutic agent is an angiogenic agent.

The Office Action stated, at page 6, 4th paragraph, that the "instant specification does not disclose the subgenus set forth in the new claims."

As explained above, the present claims do not contain a list of angiogenic agents that is a subgenus of any lists disclosed in the present application. Accordingly, it does not seem that the Office Action's comments with respect to "the subgenus set forth in the new claims" are applicable to the present claims.

In view of the above, it is respectfully requested that this rejection be withdrawn.

The rejections under 35 U.S.C. §103(a)

Claims 60, 62, 65, 67, 68, 69, 71, 72, 73, 75, 77-80, 82-84, 86, 87, 88, 90, and 91 were rejected as being obvious over U.S. Patent No. 5,879,713 (Roth) taken with U.S. Patent No. 5,869,037 (Crystal).

The Applicant respectfully traverses this rejection. The present claims contain the limitation of a polymeric **coating** comprising both an angiogenic agent and a polynucleotide encoding an angiogenic agent. Even if it were proper to combine Roth and Crystal, the combination of Roth and Crystal would not provide this limitation.

Roth does not disclose this limitation. Roth does not disclose any polymeric **coating** at all on a medical device. Instead, Roth discloses that polymeric material comprising desired substances should be loaded **in** medical devices (e.g., a balloon catheter) and then used to form a coating **on the surface of the tissue**. See col. 11, ll. 43-53:

> Local administration of a polymeric material can be performed by loading the composition **in** a balloon catheter, and then applying the composition directly to the inside of a tissue lumen within a zone occluded by the catheter balloons. The tissue surface may be an internal or external surface, and can include the interior of a tissue lumen or hollow space whether naturally occurring or occurring as a result of surgery, percutaneous techniques, trauma or disease. The polymeric material can then be reconfigured to form **a coating or "paving" layer in intimate and conforming contact with the surface**. [underscoring added]

The Applicant notes that the Office Action dated March 6, 2006 stated:

> In response to applicant's argument that Roth does not disclose a polymeric coating on a medical device, the argument is not found persuasive because Roth teaches loading the polymeric coating comprising the therapeutic agents onto a stent, which would indicate to the skilled artisan that the teaching of Roth would read on coating on a medical device.

The Office Action dated March 6, 2006 did not specify which portion of Roth was being referred to in the above quoted passage. The Applicant assumes it is the paragraph at col. 11, ll. 4-11,[2] which reads as follows:

> Preferred delivery methods are those which are minimally invasive or disruptive to the subject. These include administration of microparticles as well as percutaneous application to the interior of hollow organs or natural body cavities of a polymeric coating, film, gel, or stent. Suitable delivery devices for providing a polymer coating or layer on the surface of tissues are catheters, laparoscopes, and endoscopes, as defined in PCT/US94/94824 by Pathak et al.

There is no explicit disclosure that the polymeric coating referred to in this paragraph is present on the stent. Thus, the comment on the Office Action dated March 6, 2006 that this paragraph would suggest a "coating on a medical device" (i.e., a stent), is merely speculation. Accordingly, it should be disregarded.

Furthermore, the sentence in this paragraph containing the word "stent" reads: "These include administration of microparticles as well as percutaneous application to the interior of hollow organs or natural body cavities of a polymeric coating, film, gel, or stent." This sentence describes the application to hollow organs or body cavities of a polymeric coating, a film, a gel, **or** a stent ("... percutaneous application to the interior of hollow organs or natural body cavities of a polymeric coating, film, gel, **or** stent." [emphasis added]). The polymeric coating and the stent are disclosed as alternative substances that may be applied to the hollow organs or body cavities. There is no teaching that the polymeric coating is found on the surface of the stent.

The most natural interpretation of this passage is that it describes the common usage of a stent to prop open a hollow organ or a body cavity. This would allow the organ or cavity

[2] This is the only place in Roth where the word "stent" appears.

to remain open so that the "paving" layer described at col. 11, l. 52 could be placed on the interior of the hollow space thus formed ("The tissue surface may be an internal or external surface, and can include the interior of a tissue lumen or hollow space whether naturally occurring or occurring as a result of surgery, percutaneous techniques, trauma or disease. The polymeric material can then be reconfigured to form a coating or "paving" layer in intimate and conforming contact with the surface;" col. 11, ll. 47-53).

If instead Roth were disclosing the use of a polymeric coating on a stent, it would be expected that Roth would have taught how to apply the polymeric coating to the stent. But Roth did not.

Thus, not only is the interpretation in the Office Action dated March 6, 2006 speculation, it is implausible speculation since there is an alternative interpretation, not involving a stent with a polymeric coating, which is more in keeping with the rest of Roth's disclosure.

It should be further noted that the microparticles disclosed in Roth cannot be considered medical devices with polymeric coatings comprising an angiogenic agent and a polynucleotide encoding an angiogenic agent. Rather, Roth discloses that microparticles constitute a solid matrix in which biologically active substances are dispersed. See col. 9, ll. 24-26: "The matrix is preferably in the form of a microparticle such as a microsphere (where the biologically active molecules are dispersed throughout a solid polymeric matrix) ...").

Crystal also does not disclose a polymeric coating comprising an angiogenic agent and a polynucleotide encoding an angiogenic agent. Not only does Crystal not disclose this limitation, Crystal does not disclose a coating on a medical device at all. Crystal discloses that its vectors can be subjected to the usual techniques of pharmaceutical formulation (col.

11, ll. 14-28: "tablets, capsules, powders, granules, ointments, solutions, suppositories, injections, inhalants, and aerosols"). Crystal's working example involves injection through a syringe (col. 19, ll. 5-7: "The adenoviral vector was administered in a volume of 50 μl using a 0.5 ml syringe with a 30 gauge needle.").

In view of the lack of the disclosure of the limitation of a polymeric coating comprising an angiogenic agent and a polynucleotide encoding an angiogenic agent in both Roth and Crystal, it is respectfully requested that this rejection be withdrawn.

Claims 60, 62, 65, 66, 80, and 81 were rejected as being obvious over Roth taken with Crystal and further in view of U.S. Patent No. 5,851,521 (Branellec).

As discussed above, the combination of Roth and Crystal does not provide the limitation of a polymeric coating comprising an angiogenic agent and a polynucleotide encoding an angiogenic agent. Branellec was cited for its teaching of AAV vectors. Such teaching does not cure the defects of Roth and Crystal. Furthermore, Branellec does not disclose or suggest the limitation of a polymeric coating comprising an angiogenic agent and a polynucleotide encoding an angiogenic agent since Branellec does not disclose or suggest the combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent.

Accordingly, it is respectfully requested that this rejection be withdrawn.

Claims 60, 62, 69, 70, 84 and 85 were rejected as being obvious over Roth taken with Crystal and further in view of U.S. Patent No. 5,833,651 (Donovan).

As discussed above, the combination of Roth and Crystal does not provide the limitation of a polymeric coating comprising an angiogenic agent and a polynucleotide encoding an angiogenic agent. Donovan was cited for its teaching of metallic stents. Such teaching does not cure the defects of Roth and Crystal. Furthermore, Donovan does not disclose or suggest the limitation of a polymeric coating comprising an angiogenic agent and a polynucleotide encoding an angiogenic agent since Donovan does not disclose or suggest the combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent.

Accordingly, it is respectfully requested that this rejection be withdrawn.

Claims 60, 62, 74, 76, 89 were rejected as being obvious over Roth taken with Crystal and further in view of U.S. Patent No. 5,652,225 (Isner).

As discussed above, the combination of Roth and Crystal does not provide the limitation of a polymeric coating comprising an angiogenic agent and a polynucleotide encoding an angiogenic agent. Isner was cited for its teaching of VEGF, TGF-alpha, and TGF-beta. Such teaching does not cure the defects of Roth and Crystal. Furthermore, Isner does not disclose or suggest the limitation of a polymeric coating comprising an angiogenic agent and a polynucleotide encoding an angiogenic agent since Isner does not disclose or suggest the combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent.

Accordingly, it is respectfully requested that this rejection be withdrawn.

The time for responding to the Office Action was set for November 15, 2006. Therefore, it is believed that this response is timely. If this is in error, please treat this response as containing a Petition for the Extension of Time under 37 C.F.R. § 1.136(a) for a period sufficient to permit the filing of this paper and charge any corresponding fees to Kenyon & Kenyon's Deposit Account No. 11-0600.

The Applicant hereby also makes a Conditional Petition for any relief available to correct any defect seen in connection with this filing, or any defect seen to be remaining in this application after this filing. The Commissioner is authorized to charge Kenyon & Kenyon's Deposit Account No. 11-0600 for any fees associated with such Conditional Petition.

Respectfully submitted,
KENYON & KENYON LLP

NOVEMBER 10, 2006
Date

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APPENDIX – pending claims

1-59. (cancelled)

60. A medical device comprising:

a biocompatible structure comprising a polymeric coating that coats at least a portion of said structure, said polymeric coating comprising:

(A) a therapeutic agent, wherein said therapeutic agent is an angiogenic agent, and

(B) a vector containing a polynucleotide that establishes a gene expression sufficient to produce a therapeutically sufficient amount of one or more products encoded by said polynucleotide, wherein said polynucleotide encodes a polypeptide or protein, wherein said polypeptide or protein is an angiogenic agent.

61. (cancelled)

62. A method of controlled delivery of a genetic material to a mammalian body comprising:

(A) applying a polymer coating to at least a portion of a medical device;

(B) applying a genetic material to said polymer coating to obtain a genetically coated medical device, said genetic material comprising:

(1) a therapeutic agent, wherein said therapeutic agent is an angiogenic agent, and

(2) a vector containing a polynucleotide that establishes a gene expression sufficient to produce a therapeutically sufficient amount of one or more products encoded by said polynucleotide, wherein said polynucleotide encodes a polypeptide or protein, wherein said polypeptide or protein is an angiogenic agent,

and

(C) inserting or implanting said genetically coated medical device at a predetermined site in said mammal.

63-64. (canceled)

65. The medical device of claim 60, wherein said vector is a viral vector.

66. The medical device of claim 65, wherein said vector is an adenoassociated virus vector.

67. The medical device of claim 60, wherein said polymeric coating comprises polyurethane, silicone, EVA, poly-l-lactic acid /poly ϵ-caprolactone blends, or a combination thereof.

68. The medical device of claim 60, wherein said polymer coating is from about 1 to about 40 layers having a thickness of from about 1 to about 10 μm/ layer of coating.

69. The medical device of claim 60, wherein said structure is a stent.

70. The medical device of claim 69, wherein said stent is a metallic stent.

71. The medical device of claim 60, wherein said angiogenic agent is acidic or basic fibroblast growth factor.

72. The medical device of claim 60, wherein said angiogenic agent is vascular endothelial growth factor.

73. The medical device of claim 60, wherein said angiogenic agent is platelet-derived growth factor.

74. The medical device of claim 60, wherein said angiogenic agent is platelet-derived endothelial growth factor.

75. The medical device of claim 60, wherein said angiogenic agent is epidermal growth factor.

76. The medical device of claim 60, wherein said angiogenic agent is transforming growth factor α or β.

77. The medical device of claim 60, wherein said angiogenic agent does not include nitric oxide synthase.

78. A method of inhibiting or treating restenosis in a patient, said method comprising administering at a predetermined site within the body of said patient the device of claim 60.

79. The method of claim 78, wherein said site is a site of mechanical injury to an arterial wall produced by treatment of an atherosclerotic lesion by angioplasty.

80. The method of claim 62, wherein said vector is a viral vector.

81. The method of claim 80, wherein said vector is an adenoassociated virus vector.

82. The method of claim 62, wherein said polymeric coating comprises polyurethane, silicone, EVA, poly-l-lactic acid /poly ϵ-caprolactone blends, or a combination thereof.

83. The method of claim 62, wherein said polymer coating is from about 1 to about 40 layers having a thickness of from about 1 to about 10 μm/ layer of coating.

84. The method of claim 62, wherein said structure is a stent.

85. The method of claim 84, wherein said stent is a metallic stent.

86. The method of claim 62, wherein said angiogenic agent is acidic or basic fibroblast growth factor.

87. The method of claim 62, wherein said angiogenic agent is vascular endothelial growth factor.

88. The method of claim 62, wherein said angiogenic agent is platelet-derived growth factor.

89. The method of claim 62, wherein said angiogenic agent is platelet-derived endothelial growth factor.

90. The method of claim 62, wherein said angiogenic agent is epidermal growth factor.

91. The method of claim 62, wherein said angiogenic agent does not include nitric oxide synthase.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/542,935	04/04/2000	Maria Palasis	02844/56301	5876

26646 7590 12/08/2006

KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 12/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No. 09/542,935	Applicant(s) PALASIS, MARIA	
	Examiner Brian Whiteman	Art Unit 1635	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 14 November 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.
   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☒ *The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).*
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: *None*.
   Claim(s) objected to: *None*.
   Claim(s) rejected: *60,62 and 65-91*.
   Claim(s) withdrawn from consideration: *None*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

P. Hutchison

Continuation of 11. does NOT place the application in condition for allowance because: The amendment cannot be entered because the claims are not in compliance with 37 CFR 1.121. It is noted that the claims are listed as an appendix, but it is not apparent if the claims should be the claims of record and supplement any pending claim set. To expedite prosecution, the applicant's argument will be addressed. In view of the lengthy prosecution history of the instant application, the majority of applicant's arguments have already been addressed in a prior office action.

Priority:

In response to applicant's argument that the instant claims have support in the US patent '039 (see column 5, line 49 to column 6, line 22), the argument has already been addressed in the final rejection (pages 2-5) mailed on 8/15/06. More specifically, the specification contemplates using either a nucleic acid or a protein not both.

In response to applicant's argument that column 4, line 64 to column 5, line 48 of '039 provides support for the claims, the argument is not found persusiave because column 4, l.64 to column 5, l.48 is directed to a number of generic compounds including antisense, nucleic acids, pharmaceutically active compounds, ribozymes, proteins, and agents. There is nothing in the this paragraph that would lead one skilled in the art to products recited in the instant claims. Thus, instant claims do not enjoy priority to application 09/204,254 now US 6,369,039.

New Matter Rejection:

In response to applicant's argument that page 5, lines 3-11 provide support for the instant claims, the argument is not found persuasive because as pointed out by applicant, the instant claims limit the first therapeutic agent to a polynucleotide encoding an angiogenic agent and second therapeutic agent to an anglogenic agent.

In response to applicant's argument that page 18, line 1 provides support for the limitation missing on page 5, lines 3-11, the argument is not found persuasive because page 18, line 1 generically recites angiogenic agents and does not lead the skilled artisan to using an angiogenic protein with a polynucleotide encoding an angiogenic agent.

In response to applicant's argument that original claim 33, provides support for the instant claims, the argument is not found persuasive for the reasons of record and has already been addressed in the a previous office action (see office action page 6, mailed on 3/6/06).

In response to applicant's argument that page 22, line 21 to page 23, line 6 of the instnat specifciation provides support for the instant claims, the argument is not found persuasive because there is nothing recited in the passage that would lead the skilled artisan to claimed product.

In reponse to applicant's argument that Example 7, pages 28-29 provide using two angiogenic agents, the argument is not found persuasive because while it is acknoweldged that Example 7 uses two angiogenic agents, the agents are both polynucleotides. The working example does not lead the skilled artisan to using a polynucleotide with a protein.

In response to applicant's argument that page 5, lines 6-7 and page 6, line 9 in combination with page 17, lines 6-8 provide support for the instant claims, the argument is not found persuasive because the applicant page 5 and 6 recite a generic polynucleotide and page 17 recites a genus of non-genetic materials. There is on these passages that would the skilled artisan to the claimed product.

103 rejection:

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). This is the case here. In response to applicant's argumen that Roth *does not disclose the limitation 'polymeric coating comprising an angiogenic agent and a polynucleoitde encoding an angiogenic agent'*, the argument is not found persuasive because the combination of Donovan and Crystal teach polymeric coating comprisng a polynucleotide encoding angiogenic protein and an angiogenic protein.

In response to applicant's argument that Donovan does not teach a polymeric coating on a stent, the argument is not found persuasive *because applicant is aruging against the references individually (In re Keller). Furthermore, the only claims that recite stent are claims 69,* 70, 84, and 85 and the rest of the claims do not recite stent. Donovan teaches a microparticle (allowing controlled release of biologically active substance) comprising a polymer and a biologically active substance (columns 16-18), which reads on the structure recited in claims 60, 62, 65-68, 71-83, and 86-89.

The argument against Roth taken with Crystal in further view of either Donovan or Branellec are based on the same arguments against Roth taken with Crystal and are not found persuasive for the reasons of record.

Notice of Non-Compliant Amendment (37 CFR 1.121)	Application No. 09/542,935	Applicant(s) PALASIS, MARIA	
	Examiner Brian Whiteman	Art Unit 1635	

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

The amendment document filed on *14 November 2006* is considered non-compliant because it has failed to meet the requirements of 37 CFR 1.121 or 1.4. In order for the amendment document to be compliant, correction of the following item(s) is required.

THE FOLLOWING MARKED (X) ITEM(S) CAUSE THE AMENDMENT DOCUMENT TO BE NON-COMPLIANT:

- ☐ 1. Amendments to the specification:
  - ☐ A. Amended paragraph(s) do not include markings.
  - ☐ B. New paragraph(s) should not be underlined.
  - ☐ C. Other _____.
- ☐ 2. Abstract:
  - ☐ A. Not presented on a separate sheet. 37 CFR 1.72.
  - ☐ B. Other _____.
- ☐ 3. Amendments to the drawings:
  - ☐ A. The drawings are not properly identified in the top margin as "Replacement Sheet," "New Sheet," or "Annotated Sheet" as required by 37 CFR 1.121(d).
  - ☐ B. The practice of submitting proposed drawing correction has been eliminated. Replacement drawings showing amended figures, without markings, in compliance with 37 CFR 1.84 are required.
  - ☐ C. Other _____.
- ☒ 4. Amendments to the claims:
  - ☐ A. A complete listing of all of the claims is not present.
  - ☐ B. The listing of claims does not include the text of all pending claims (including withdrawn claims)
  - ☒ C. Each claim has not been provided with the proper status identifier, and as such, the individual status of each claim cannot be identified. Note: the status of every claim must be indicated after its claim number by using one of the following status identifiers: (Original), (Currently amended), (Canceled), (Previously presented), (New), (Not entered), (Withdrawn) and (Withdrawn-currently amended).
  - ☐ D. The claims of this amendment paper have not been presented in ascending numerical order.
  - ☐ E. Other: _____.
- ☐ 5. Other (e.g., the amendment is unsigned or not signed in accordance with 37 CFR 1.4):

For further explanation of the amendment format required by 37 CFR 1.121, see MPEP § 714.

TIME PERIODS FOR FILING A REPLY TO THIS NOTICE:

1. Applicant is given **no new time period** if the non-compliant amendment is an after-final amendment or an amendment filed after allowance. If applicant wishes to resubmit the non-compliant after-final amendment with corrections, the **entire corrected amendment** must be resubmitted.
2. Applicant is given **one month**, or thirty (30) days, whichever is longer, from the mail date of this notice to supply the correction, if the non-compliant amendment is one of the following: a preliminary amendment, a non-final amendment (including a submission for a request for continued examination (RCE) under 37 CFR 1.114), a supplemental amendment filed within a suspension period under 37 CFR 1.103(a) or (c), and an amendment filed in response to a *Quayle* action. If any of above boxes 1. to 4. are checked, the correction required is only the **corrected section** of the non-compliant amendment in compliance with 37 CFR 1.121.

   Extensions of time are available under 37 CFR 1.136(a) only if the non-compliant amendment is a non-final amendment or an amendment filed in response to a *Quayle* action.

   Failure to timely respond to this notice will result in:
   Abandonment of the application if the non-compliant amendment is a non-final amendment or an amendment filed in response to a *Quayle* action; or
   Non-entry of the amendment if the non-compliant amendment is a preliminary amendment or supplemental amendment.

Legal Instruments Examiner (LIE), if applicable _____ Telephone No. _____

[Attorney Docket: 12013/56301]

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor : Maria PALASIS	Art Unit : 1635
Serial No.: 09/542,935	Examiner : B. Whiteman
Filing Date: April 4, 2000	
For: Insertable or Implantable Medical Devices Suitable for Gene Therapy Regimens	

MAIL STOP AF
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT UNDER 37 C.F.R. §1.116

SIR:

In response to the Office Action dated July 22, 2005 containing a Final Rejection, Applicants request a one-month extension of time extending the period of response up to and including November 22, 2005. The Office is authorized to charge the one-month extension of time fee to Kenyon & Kenyon's Deposit Account No. 11-0600. Applicants request entry of the following amendments and request reconsideration of the present application. Enclosed herewith is a Notice of Appeal.

Amendments to the Claims:

1-59. (cancelled)

60. (currently amended) A medical device comprising:

a biocompatible structure comprising a polymeric coating that coats at least a portion of said structure, said polymeric coating comprising:

(A) a therapeutic agent, wherein said therapeutic agent ~~selected from the group consisting of~~

~~(1)~~ is an angiogenic agent,

~~(2) an agent that enhances gene transfer and integration into tissue and cells;~~

~~(3) a immunosuppressant;~~

~~(4) an antiangiogenic agent;~~

~~(5) an antithrombogenic agent;~~

~~(6) tissue plasminogen activator;~~

~~(7) erythropoietin;~~

~~(8) an antioxidant;~~

~~(9) an agent blocking smooth muscle proliferation;~~

~~(10) an anti-inflammatory agent;~~

~~(11) a calcium entry blocker;~~

~~(12) an antineoplastic,~~

~~(13) an antiproliferative or anti-mitotic agent;~~

~~(14) an anesthetic agent;~~

~~(15) an anticoagulant;~~

~~(16) an anti-thrombin antibody;~~

~~(17) an anti-platelet receptor antibody;~~

~~(18) a prostaglandin inhibitor;~~

~~(19) a platelet inhibitor;~~

~~(20) a vascular cell growth promoter;~~

~~(21) a growth factor receptor antagonist;~~

~~(22) a transcriptional activator;~~

~~(23) a translational promoter;~~

~~(24) a vascular cell growth inhibitor;~~

~~(25) a growth factor receptor antagonist;~~

~~(26) a transcriptional repressor;~~

~~(27) a translational repressor;~~

~~(28) a replication inhibitor;~~

~~(29) an inhibitory antibody;~~

~~(30) an antibody directed against a growth factor;~~

~~(31) a bifunctional molecule consisting of a growth factor and a cytotoxin;~~

~~(32) a cholesterol lowering agent;~~

~~(33) a vasodilating agent;~~

~~(34) an agent which interferes with endogenous vasoactive mechanisms; and~~

~~(35) a cell cycle inhibitors;~~

and

(B) a vector containing a polynucleotide that establishes a gene expression sufficient to produce a therapeutically sufficient amount of one or more products encoded by said polynucleotide, wherein said polynucleotide encodes a polypeptide or protein, wherein said polypeptide or protein ~~selected from the group consisting of~~

~~(1)~~ is an angiogenic agent~~;~~

~~(2) an antiangiogenic agent;~~

~~(3) an antithrombogenic agent;~~

~~(4) tissue plasminogen activator;~~

~~(5) erythropoietin;~~

~~(6) an antioxidant;~~

~~(7) an agent blocking smooth muscle proliferation;~~

~~(8) an anti-inflammatory agent;~~

~~(9) a calcium entry blocker;~~

~~(10) an antineoplastic;~~

~~(11) an antiproliferative or anti-mitotic agent;~~

~~(12) an anesthetic agent;~~

~~(13) an anticoagulant;~~

~~(14) an anti-thrombin antibody;~~

~~(15) an anti-platelet receptor antibody;~~

~~(16) a prostaglandin inhibitor;~~

~~(17) a platelet inhibitor;~~

~~(18) a vascular cell growth promoter;~~

~~(19) a growth factor receptor antagonist;~~

~~(20) a transcriptional activator;~~

~~(21) a translational promoter;~~

~~(22) a vascular cell growth inhibitor;~~

~~(23) a growth factor receptor antagonist;~~

~~(24) a transcriptional repressor;~~

~~(25) a translational repressor;~~

~~(26) a replication inhibitor;~~

~~(27) an inhibitory antibody;~~

~~(28) an antibody directed against a growth factor;~~

~~(29) a bifunctional molecule consisting of a growth factor and a cytotoxin;~~

~~(30) a cholesterol lowering agent;~~

~~(31) a vasodilating agent;~~

~~(32) an agent which interferes with endogenous vasoactive mechanisms;~~

~~(33) an anti-restenosis agent;~~

~~(34) a monocyte chemoattractant protein;~~

~~(35) a bone morphogenic protein;~~

~~(36) a hedgehog protein and~~

~~(37) a cell cycle inhibitors;~~

~~wherein the angiogenic agent is an acidic fibroblast growth factor, basic fibroblast growth factor, vascular endothelial growth factor, epidermal growth factor, transforming growth factor α and β, platelet derived endothelial growth factor, platelet derived growth factor, tumor necrosis factor α, hepatocyte growth factor, or insulin growth factor~~.

61. (cancelled)

62. (currently amended) A method of controlled delivery of a genetic material to a mammalian body comprising:

(A) applying a polymer coating to at least a portion of a medical device;

(B) applying a genetic material to said polymer coating to obtain a genetically coated medical device, said genetic material comprising:

~~(A)~~ (1) a therapeutic agent, wherein said therapeutic agent ~~selected from the group consisting of~~

~~(1)~~ is an angiogenic agent,

~~(2) an agent that enhances gene transfer and integration into tissue and cells;~~

~~(3) a immunosuppressant;~~

~~(4) an antiangiogenic agent;~~

~~(5) an antithrombogenic agent;~~

~~(6) tissue plasminogen activator;~~

~~(7) erythropoietin;~~

~~(8) an antioxidant;~~

~~(9) an agent blocking smooth muscle proliferation;~~

~~(10) an anti-inflammatory agent;~~

~~(11) a calcium entry blocker;~~

~~(12) an antineoplastic,~~

~~(13) an antiproliferative or anti-mitotic agent;~~

~~(14) an anesthetic agent;~~

~~(15) an anticoagulant;~~

~~(16) an anti-thrombin antibody;~~

~~(17) an anti-platelet receptor antibody;~~

~~(18) a prostaglandin inhibitor;~~

~~(19) a platelet inhibitor;~~

~~(20) a vascular cell growth promoter;~~

~~(21) a growth factor receptor antagonist;~~

~~(22) a transcriptional activator;~~

~~(23) a translational promoter;~~

~~(24) a vascular cell growth inhibitor;~~

~~(25) a growth factor receptor antagonist;~~

~~(26) a transcriptional repressor;~~

~~(27) a translational repressor;~~

~~(28) a replication inhibitor;~~

~~(29) an inhibitory antibody;~~

~~(30) an antibody directed against a growth factor;~~

~~(31) a bifunctional molecule consisting of a growth factor and a cytotoxin;~~

~~(32) a cholesterol-lowering agent;~~

~~(33) a vasodilating agent;~~

~~(34) an agent which interferes with endogenous vasoactive mechanisms; and~~

~~(35) a cell cycle inhibitors;~~

and

~~(B)~~ (2) a vector containing a polynucleotide that establishes a gene expression sufficient to produce a therapeutically sufficient amount of one or more products encoded by said polynucleotide, wherein said polynucleotide encodes a polypeptide or protein, wherein said polypeptide or protein ~~selected from the group consisting of~~

~~(1)~~ is an angiogenic agent,

~~(2) an antiangiogenic agent;~~

~~(3) an antithrombogenic agent;~~

~~(4) tissue plasminogen activator;~~

~~(5) erythropoietin;~~

~~(6) an antioxidant;~~

~~(7) an agent blocking smooth muscle proliferation;~~

~~(8) an anti-inflammatory agent;~~

~~(9) a calcium entry blocker;~~

~~(10) an antineoplastic,~~

~~(11) an antiproliferative or anti-mitotic agent;~~

~~(12) an anesthetic agent;~~

~~(13) an anticoagulant;~~

~~(14) an anti-thrombin antibody;~~

~~(15) an anti-platelet receptor antibody;~~

~~(16) a prostaglandin inhibitor;~~

~~(17) a platelet inhibitor;~~

~~(18) a vascular cell growth promoter;~~

~~(19) a growth factor receptor antagonist;~~

~~(20) a transcriptional activator;~~

~~(21) a translational promoter;~~

~~(22) a vascular cell growth inhibitor;~~

~~(23) a growth factor receptor antagonist;~~

~~(24) a transcriptional repressor;~~

~~(25) a translational repressor;~~

~~(26) a replication inhibitor;~~

~~(27) an inhibitory antibody;~~

~~(28) an antibody directed against a growth factor;~~

~~(29) a bifunctional molecule consisting of a growth factor and a cytotoxin;~~

~~(30) a cholesterol lowering agent;~~

~~(31) a vasodilating agent;~~

~~(32) an agent which interferes with endogenous vasoactive mechanisms; and~~

~~a cell cycle inhibitors~~

~~(33) an anti-restenosis agent;~~

~~(34) a monocyte chemoattractant protein;~~

~~(35) a bone morphogenic protein;~~

~~(36) a hedgehog protein and~~

~~(37) a cell cycle inhibitors;~~

~~wherein the angiogenic agent is an acidic fibroblast growth factor, basic fibroblast growth factor, vascular endothelial growth factor, epidermal growth factor, transforming growth factor α and β, platelet-derived endothelial growth factor, platelet-derived growth factor, tumor necrosis factor α, hepatocyte growth factor, or insulin growth factor;~~ and

(C) inserting or implanting said genetically coated medical device at a predetermined site in said mammal.

63-64. (canceled)

65. (new) The medical device of claim 60, wherein said vector is a viral vector.

66. (new) The medical device of claim 65, wherein said vector is an adenoassociated virus vector.

67. (new) The medical device of claim 60, wherein said polymeric coating comprises polyurethane, silicone, EVA, poly-l-lactic acid /poly ε-caprolactone blends, or a combination thereof.

68. (new) The medical device of claim 60, wherein said polymer coating is from about 1 to about 40 layers having a thickness of from about 1 to about 10 μm/ layer of coating.

69. (new) The medical device of claim 60, wherein said structure is a stent.

70. (new) The medical device of claim 69, wherein said stent is a metallic stent.

71. (new) The medical device of claim 60, wherein said angiogenic agent is acidic or basic fibroblast growth factor.

72. (new) The medical device of claim 60, wherein said angiogenic agent is vascular endothelial growth factor.

73. (new) The medical device of claim 60, wherein said angiogenic agent is platelet-derived growth factor.

74. (new) The medical device of claim 60, wherein said angiogenic agent is platelet-derived endothelial growth factor.

75. (new) The medical device of claim 60, wherein said angiogenic agent is epidermal growth factor.

76. (new) The medical device of claim 60, wherein said angiogenic agent is transforming growth factor α or β.

77. (new) The medical device of claim 60, wherein said angiogenic agent does not include nitric oxide synthase.

78. (new) A method of inhibiting or treating restenosis in a patient, said method comprising administering at a predetermined site within the body of said patient the device of claim 60.

79. (new) The method of claim 78, wherein said site is a site of mechanical injury to an arterial wall produced by treatment of an atherosclerotic lesion by angioplasty.

80. (new) The method of claim 62, wherein said vector is a viral vector.

81. (new) The method of claim 80, wherein said vector is an adenoassociated virus vector.

82. (new) The method of claim 62, wherein said polymeric coating comprises polyurethane, silicone, EVA, poly-l-lactic acid /poly ε-caprolactone blends, or a combination thereof.

83. (new) The method of claim 62, wherein said polymer coating is from about 1 to about 40 layers having a thickness of from about 1 to about 10 μm/ layer of coating.

84. (new) The method of claim 62, wherein said structure is a stent.

85. (new) The method of claim 84, wherein said stent is a metallic stent.

86. (new) The method of claim 62, wherein said angiogenic agent is acidic or basic fibroblast growth factor.

87. (new) The method of claim 62, wherein said angiogenic agent is vascular endothelial growth factor.

88. (new) The method of claim 62, wherein said angiogenic agent is platelet-derived growth factor.

89. (new) The method of claim 62, wherein said angiogenic agent is platelet-derived endothelial growth factor.

90. (new) The method of claim 62, wherein said angiogenic agent is epidermal growth factor.

91. (new) The method of claim 62, wherein said angiogenic agent does not include nitric oxide synthase.

REMARKS

Before this Amendment, claims 3, 10-12, 17-20, 23-25, 27, 34-38, 42-44, 47, 54-55, 58-60, and 62-64 were pending. By this Amendment, claims 3, 10-12, 17-20, 23-25, 27, 34-38, 42-44, 47, 54-55, 58-59, and 63-64 have been canceled and new claims 65-91 have been added. Therefore, if this Amendment is entered, an equal number of dependent claims will have been canceled and added and claims 60, 62, and 65-91 will be pending. It is believed that the added dependent claims all read on the elected species "angiogenic agent." In view of the above, the Applicant submits that it is appropriate to enter this Amendment.

Claims 60 and 62 have been amended to delete the recitation of non-elected species. Claims 60 and 62 now recite a combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent. Support for such a combination is found in the specification, as discussed below in the section directed to the rejections under 35 U.S.C. §112.

Support for new claims 65-91 is as follows:

New claims 65, 66, 67, 68, 69, 70, 78, 79, 80, 81, 82, 83, 84, and 85 correspond to prior claims 10, 3, 17, 18, 19, 20, 24, 25, 34, 27, 42, 43, 44, 47, respectively. These prior claims have been deleted and these new claims added to address the objection in the Office Action that these prior claims did not depend from a preceding claim. New claims 65, 66, 67, 68, 69, 70, 78, 79, 80, 81, 82, 83, 84, and 85 all depend from a preceding claim.

New claims 71-76 and 86-90 recite particular angiogenic agents. Support for the recitation of these particular angiogenic agents is found in the specification as follows:

Claims 71 and 86, page 18, lines 19-20.

Claims 72 and 87, page 18, line 20.

Claims 73 and 88, page 18, line 22.

Claims 74 and 89, page 18, line 21.

Claims 75 and 90, page 18, lines 20-21.

Claim 76, page 18, line 21.

Claims 77 and 91 recite that the angiogenic agent does not include nitric oxide synthase. Support for this recitation is found in the specification, at page 17, line 19 to page 18, line 16, where alternative therapeutic agents are positively recited: "Non-limiting examples of products and therapeutic agents of the invention include: ... nitric oxide synthase (NOS) ..." Such positive recitation nitric oxide as an alternative therapeutic agent provides support for a negative limitation with respect to nitric oxide synthase. See M.P.E.P. §2173.05(i):

> Any negative limitation or exclusionary proviso must have basis in the original disclosure. *If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims*. See *In re Johnson*, 558 F.2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977) ("[the] specification, having described the whole, necessarily described the part remaining."). See also *Ex parte Grasselli*, 231 USPQ 393 (Bd. App. 1983), *aff'd mem.*, 738 F.2d 453 (Fed. Cir. 1984). (Emphasis added)

Election/Restrictions

The Office Action stated that species (2)-(35) and (2)-(37) in claims 60 and 62 were directed to non-elected subject matter.

Claims 60 and 62 have been amended to omit recitation of species (2)-(35) and (2)-(37).

Priority

The Office Action stated that the previous claims are not entitled to the priority date of U.S. Patent Application Serial No. 09/204,254 (now U.S. Patent No. 6,369,039) because "nothing in the specification [of U.S. Patent Application Serial No. 09/204,254] would lead one to the particular combination" of angiogenic agents set forth in the previous claims and therefore U.S. Patent Application Serial No. 09/204,254 lacks a written description of the previous claims (Office Action, paragraph bridging pages 3 and 4).

The claims have been amended to delete recitation of the combination of angiogenic agents recited in the previous claims. All the claims now recite a combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent. To illustrate this, currently amended claim 60 is reproduced below, without the markings showing how it has been amended.

> 60. A medical device comprising:
> a biocompatible structure comprising a polymeric coating that coats at least a portion of said structure, said polymeric coating comprising:
> (A) a therapeutic agent, where said therapeutic agent is an angiogenic agent, and
> (B) a vector containing a polynucleotide that establishes a gene expression sufficient to produce a therapeutically sufficient amount of one or more products encoded by said

polynucleotide, wherein said polynucleotide encodes a polypeptide or protein, where said polypeptide or protein is an angiogenic agent.

The combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent is disclosed in the paragraph at col. 5, l. 49 to col. 6, l. 22 of U.S. Patent No. 6,369,039, which reads in relevant part: "In addition, the polypeptides or proteins that can be incorporated into the polymer coating 130, or whose DNA can be incorporated, include without limitation, angiogenic factors ... and combinations thereof."

The combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent is also disclosed in the paragraph at col.4, l. 64 to col. 5, l. 48. This paragraph teaches which therapeutic agents can be in the coating. Polynucleotides (col. 4, l. 67 to col. 5, l. 4) and angiogenic agents (col. 5, ll. 15-16) are taught. The combination of polynucleotides and angiogenic agents is taught at col. 5, l. 44 ("and combinations thereof"). That the polynucleotides may encode angiogenic agents is taught at col. 5, ll. 62-65.

The present claims are therefore entitled to the priority date of U.S. Patent Application Serial No. 09/204,254 (now U.S. Patent No. 6,369,039).

Claim objections

The claims were objected to because the dependent claims did not depend from a preceding claim.

The claims have been amended so that all dependent claims depend from a preceding claim.

Claims 37 and 58 were objected to as being substantial duplicates.

Claims 37 and 58 have been canceled.

The rejection under 35 U.S.C. §112

The claims were rejected for failure to comply with the written description requirement because the "instant specification does not disclose the subgenus" of angiogenic agents set forth in the claims (Office Action, sentence bridging pages 6-7 and following sentence).

The claims have been amended and no longer recite the subgenus of angiogenic agents to which this rejection was directed. The claims as presently amended have written description support since the specification provides guidance which clearly leads the skilled person to the recited combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent.

The combination of a therapeutic agent comprising genetic material, e.g., a polynucleotide, with a non-genetic therapeutic agent is clearly disclosed at page 17, lines 6-8:

> The first therapeutic agent of this invention comprises genetic materials whereas the second therapeutic agent of the invention may comprise either genetic or non-genetic materials.

The reference to the "first therapeutic agent" in this passage would be understood in light of prior disclosures in the specification which teach that the "first therapeutic agent" is preferably a polynucleotide. See, e.g., page 5, lines 6-7 ("a first therapeutic agent comprising ... a first polynucleotide ..."); page 6, line 9 ("a first therapeutic agent comprising ... a first polynucleotide ..."). Thus, the passage at page 17, lines 6-8 would be understood as teaching the combination of a first therapeutic agent that is a polynucleotide with a non-genetic therapeutic agent.

In the second paragraph after the above disclosure of the combination of a first therapeutic agent that is a polynucleotide with a non-genetic therapeutic agent, there is a disclosure that both therapeutic agents can be angiogenic agents (page 18, line 1).

This is reinforced by original claim 33, which states that "said first therapeutic agent, said second therapeutic agent, ***or both***" can lead to the production of an angiogenic agent. Original claim 33 depends from original claim 26, which, in one of its embodiments, is directed to the combination of a polynucleotide and a protein. Thus, original claim 33 teaches that the Applicant contemplated the combination of a polynucleotide and a protein where the polynucleotide encodes an angiogenic agent and the protein is an angiogenic agent.

The skilled person is again directed to this combination at page 22, line 21 to page 23, line 6, where a preferred embodiment of the invention is disclosed as:

> A preferred embodiment of this invention is to provide treatment of vascular thrombosis and angioplasty restenosis, particularly coronary vascular thrombosis, and angioplasty restenosis, thereby to decrease incidence of vessel rethrombosis and restenosis, unstable angina, myocardial infarction and sudden death. The medical device and method of this invention can be used to treat patients having severe complications resulting from thrombus. Specific examples include patients with acute myocardial infarction (AMI) and patients that have failed PTCA (percutaneous transluminal coronary angioplasty) and have abrupt thrombotic closure of the targeted artery.

From this passage, the skilled person would recognize that the invention is designed to increase blood flow and thereby oxygen delivery to tissues, particularly to tissues sensitive to disruptions in cardiovascular perfusion. The skilled person would recognize that this can be accomplished through a local increase of blood flow by the development and expansion of blood vessels in an area of potential stenosis or thrombotic blockage, i.e., by angiogenesis. Thus, the skilled person is directed to the choice of "angiogenic agents" as the therapeutic agents of the invention.

Furthermore, in Example 7 on pages 28-29, the specification discloses an embodiment in which both therapeutic agents are "angiogenic agents." This example discloses a medical device comprising polynucleotides encoding VEGF protein and FAS Ligand protein.

The specification indicates that VEGF protein is a "promoter of endothelialization" (Example 7, page 29, line 3), i.e., an angiogenic agent. Moreover, it is well known in the art that VEGF protein is known to play a critical and central role in angiogenesis. FAS Ligand is also known to promote angiogenesis. See Biancone et al., Development of Inflammatory Angiogenesis by Local Stimulation of Fas In Vivo. J. Exp. Med. Volume 186, Number 1, July 7, 1997 147-152 (see, e.g., the summary, at page 147: "These findings suggest a role for Fas-Fas ligand interaction in promoting local angiogenesis and inflammation.")

Thus, Example 7 clearly directs the skilled person to the concept of practicing the invention wherein ***both*** therapeutic agents are angiogenic agents. Although Example 7 describes the use of two genetic therapeutic agents rather than the presently claimed combination of a genetic therapeutic agent and a non-genetic therapeutic agent, the combination of a genetic therapeutic agent and a non-genetic therapeutic agent is clearly described elsewhere (see discussion above) and would have been understood as being applicable to the teaching of Example 7 that both therapeutic agents can be angiogenic agents.

In view of the disclosures of the application discussed above, it is clear that the combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent is described in the application. Therefore, the present claims have written description support and it is respectfully requested that this rejection be withdrawn.

The rejection under 35 U.S.C. §102

Certain of the previous claims were rejected as being anticipated by U.S. Patent No. 5,879,713 (Roth).

The Applicant respectfully traverses this rejection. The present claims require a polymeric coating on at least a portion of a medical device. Roth does not disclose a polymeric coating on a medical device. Instead, Roth discloses that a medical device (e.g., a catheter) can be used to deliver a polymer to a tissue so as to form a coating on the surface of the tissue. See col. 11, ll. 43-53:

> Local administration of a polymeric material can be performed by loading the composition in a balloon catheter, and then applying the composition directly to the inside of a tissue lumen within a zone occluded by the catheter balloons. The tissue surface may be an internal or external surface, and can include the interior of a tissue lumen or hollow space whether naturally occurring or occurring as a result of surgery, percutaneous techniques, trauma or disease. The polymeric material can then be reconfigured to form a coating or "paving" layer in intimate and conforming contact with the surface.

The claims have been amended and now recite a combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent. Roth does not disclose this combination. Specifically, although Roth states that biologically active molecules include proteins, nucleic acid molecules, carabohydrates and "combinations thereof," Roth does not describe the specific combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent, as recited by the present claims. Accordingly, Roth does not anticipate the present claims. Thus, it is respectfully requested that this rejection be withdrawn.

The Applicant notes that the present claims are not anticipated by U.S. Patent No. 5,652,225 (Isner). With the exception of one paragraph, the entire disclosure of Isner is directed to the use of hydrophilic polymers incorporating a single DNA encoding a protein, e.g., an angiogenic protein.

The exceptional paragraph occurs at col. 7, ll. 1-10. In this paragraph, Isner describes three additional methods of practicing his invention. The three methods involve certain combinations of DNA encoding angiogenic factors, DNA encoding non-angiogenic factors, angiogenic factors, and non-angiogenic factors.

> In certain situations, it may be desirable to use DNA's [sic] encoding two or more different proteins in order [sic] optimize the therapeutic outcome. For example, DNA encoding two angiogenic proteins, e.g., VEGF and bFGF, can be used, and provides an improvement over the use of bFGF alone. Or an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells, while simultaneously including angiogenesis, ...

The three methods described in this paragraph are:

Method 1: DNAs encoding two angiogenic proteins, i.e.,

DNA encoding an angiogenic factor + DNA encoding an angiogenic factor

Method 2: an angiogenic factor combined with other genes, i.e.,

An angiogenic factor + DNA encoding a non-angiogenic factor

Method 3: an angiogenic factor combined with gene products of other genes, i.e.,

An angiogenic factor + a non-angiogenic factor

The present claims all require the combination of a polynucleotide (e.g., DNA) encoding an angiogenic agent[1] with an angiogenic agent, i.e., an angiogenic factor + DNA encoding an angiogenic factor.

None of Isner's three methods is directed to an angiogenic factor + DNA encoding an angiogenic factor. This is shown in the following table. In the table, each of the possible combinations of DNA encoding angiogenic factors, DNA encoding non-angiogenic factors, angiogenic factors, and non-angiogenic factors is represented by an entry at the intersection of the corresponding terms at the top and side of the table.

[1] For the purposes of this discussion, it is assumed that the term "angiogenic factor" used by Isner is the same as the term "angiogenic agent" as used in the present claims.

	DNA encoding angiogenic factors	DNA encoding non-angiogenic factors	angiogenic factors	non-angiogenic factors
DNA encoding angiogenic factors	Isner method 1		***The present claims***	
DNA encoding non-angiogenic factors			Isner method 2	
angiogenic factors	***The present claims***	Isner method 2		Isner method 3
non-angiogenic factors			Isner method 3	

It can be seen at a glance that there is no overlap between Isner and the present claims.

Isner goes on to provide a list of some of the products that can be used in his three methods: "including, for example, nitric oxide synthase, L-argine, [sic] fibronectin, urokinase, plasminogen activator and heparin (col. 7, ll. 9-10)."

The Applicant notes that nitric oxide synthase is not an "angiogenic agent" as that term is used in the present application. This can be understood from the manner in which these terms are used in the present application.

• Angiogenic agents and nitric oxide synthase are listed separately in the list of products and therapeutic agents of the invention at page 17, line 20 to page 18, line 17. Angiogenic agents are recited at page 18, line 1 while nitric oxide synthase is recited later, at page 18, line 6, in the midst of anesthetics and anti-coagulants, i.e., products that are undeniably not angiogenic agents. Such listings make no sense if nitric oxide synthase is an angiogenic agent.

• Page 18, line 18 to page 19, line 1, provides a list of angiogenic agents ("acidic and basic fibroblast growth factors, vascular endothelial growth factor, epidermal growth factor, transforming growth factor α and β, platelet-derived endothelial growth factor, platelet-

derived growth factor, tumor necrosis factor α, hepatocyte growth factor and insulin like growth factor"). Nitric oxide synthase is not part of this list.

• Where the present invention provides examples of the use of nitric oxide synthase, nitric oxide synthase is not used an angiogenic agent. Example 6 of the present application (pages 27-28) describes three experiments in which nitric oxide synthase is used for purposes other than angiogenesis (i.e., creating new blood vessels). In experiment 1 (page 27, line 21 to page 28, line 1), nitric oxide synthase is used to prevent restenosis. In experiment 2 (page 28, lines 2-6,), nitric oxide synthase is used to prevent progression and promote the healing of atherosclerotic lesions. In experiment 3 (page 28, lines 7-12), nitric oxide synthase is used to promote cell death in anti-cancer therapy.

Even assuming, *arguendo*, that nitric oxide synthase is considered to be an angiogenic agent by the art, the above teachings of the application make clear that nitric oxide synthase is not an "angiogenic agent" for the purposes of the present invention. The Applicant has been her own lexicographer and has defined the term "angiogenic agent" by implication so as to exclude nitric oxide synthase. Thus, any disclosure of nitric oxide synthase in Isner is not relevant to the present claims.

Even if nitric oxide synthase is considered to be an angiogenic agent, this would not mean that Isner discloses the present invention. If nitric oxide synthase is considered to be an angiogenic agent then it could serve the following roles in the three methods disclosed in Isner:

• either as one or both of the products encoded by the two DNAs of method 1

• as the angiogenic factor that is combined with "other genes" in method 2

• as the angiogenic factor that is combined with the gene products of "other genes" in method 3

In none of these cases would the result be within the scope of the present claims. In no case would the result be an angiogenic agent combined with a DNA encoding an angiogenic agent.

Furthermore, Isner does not anticipate claims 71-76 and 86-90, which are directed to combinations of particular angiogenic agents with DNA encoding those particular angiogenic agents since Isner does not disclose such combinations.

In view of the above, it is clear that Isner does not anticipate the present claims.

The rejections under 35 U.S.C. §103

Certain of the previous claims were rejected as being obvious over Roth taken together with U.S. Patent No. 5,851,521 (Branellec).

The claims have been amended and now recite a combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent. As discussed above, Roth does not disclose this combination. Branellec also does not disclose this combination. Since Roth and Branellec lack a disclosure of this combination, and also lack any suggestion to make this combination, Roth and Branellec do not make obvious the present claims. Thus, it is respectfully requested that this rejection be withdrawn.

Certain of the previous claims were rejected as being obvious over Roth taken together with U.S. Patent No. 5,851,521 (Branellec) and further in view of Vincent-Lacaze et al., 1999, J. Virol. 73:1949-1955 (Vincent-Lacaze).

The claims have been amended and now recite a combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent. As discussed above, Roth and Branellec do not disclose this combination. Vincent-Lacaze also does not disclose this combination. Since Roth, Branellec, and Vincent-Lacaze lack a disclosure of this combination, and also lack any suggestion to make this combination, Roth, Branellec, and Vincent-Lacaze do not make obvious the present claims. Thus, it is respectfully requested that this rejection be withdrawn.

Certain of the previous claims were rejected as being obvious over Roth taken together with U.S. Patent No. 5,833,651 (Donovan).

The claims have been amended and now recite a combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent. As discussed above, Roth does not disclose this combination. Donovan also does not disclose this combination. Since Roth and Donovan lack a disclosure of this combination, and also lack any suggestion to make this combination, Roth and Donovan do not make obvious the present claims. Thus, it is respectfully requested that this rejection be withdrawn.

The Office is authorized to charge any fees or credit any overpayments that may be associated with the filing of this paper to Kenyon & Kenyon's Deposit Account No. 11-0600. The Applicant hereby also makes a Conditional Petition for any relief available to correct any defect seen in connection with this filing, or any defect seen to be remaining in this

application after this filing. The Commissioner is authorized to charge Kenyon & Kenyon's Deposit Account No. 11-0600 for any fees associated with such Conditional Petition.

Respectfully submitted,
KENYON & KENYON

ZEBA Ali for

11-17-05
Date

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/542,935	04/04/2000	Maria Palasis	02844/56301	5876

26646 7590 12/12/2005

KENYON & KENYON
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NEW YORK, NY 10004

EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 12/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

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Advisory Action Before the Filing of an Appeal Brief	Application No. 09/542,935	Applicant(s) PALASIS, MARIA	
	Examiner Brian Whiteman	Art Unit 1635	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 17 November 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *17 November 2005*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☒ They raise the issue of new matter (see NOTE below);
   (c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *None*.

   Claim(s) objected to: *None*.

   Claim(s) rejected: *3,10-12,17-20,23-25,27,34-38,42-44,47,54,55,58-60 and 62-64*.

   Claim(s) withdrawn from consideration: *None*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

Joe Woitach
AU 1635

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Continuation of 3. NOTE: The proposed deletion of the angiogenic agents in claims 60 and 62 and the proposed addition of new claims 71-77 and 86-91 that placed some of the angiogenic agents in claims 60 and 62 into separate claims would raise an issue of new matter and require a new search and further consideration.

Continuation of 11. does NOT place the application in condition for allowance because: In response to applicant's argument that Roth does not disclose a polymeric coating on a medical device (See Col. 11, lines 43-53), the argument is not found persuasive because Roth teaches a medical device comprising polymeric carrier comprising biologically active molecule (columns 3 and 8-10).
In response to applicant's argument that the claims have been amended to recite a combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent, the argument is not found persuasive because the claims already recited this limitation and have been rejected based on this limitation.
In response to applicant's argument that Roth does not disclose the combination recited in the claim, the argument is not found persuasive because Roth teaches biologically active molecules include proteins, growth factors, and angiogenic factors and DNA encoding them (columns 9-10). In addition, the term "angiogenic agent" in (A) of claims 60 and 62 is broader than a protein because the term has replaced "non-genetic therapeutic agent" that was part of the election of species and recited in the original claims.
The argument against Isner is moot because Isner was not recited in a prior art rejection.
The arguments against the 103 rejections are not found persuasive because the arguments were based on arguments that were already addressed above.

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Request For Continued Examination (RCE) Transmittal

Address to:
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Application Number	09/542,935
Filing Date	April 4, 2000
First Named Inventor	M. PALASIS
Art Unit	1635
Examiner Name	B. Whiteman
Attorney Docket Number	12013/56301

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 C.F.R. 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

a. ☒ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
ii. ☐ Other _____

b. ☐ Enclosed

i. ☐ Amendment/Reply
ii ☐ Affidavit(s)/Declaration(s)
iii. ☐ Information Disclosure Statement (IDS)
iv. ☐ Other _____

2. Miscellaneous

a. ☐ Suspension of action on the above-identified application is requested under 37 C.F.R. 1.103(c) for a period of _____months. (Period of suspension shall not exceed 3 months; Fee under 37 C.F.R. 1.17(i) required)

b. ☐ Other _____

3. Fees The RCE fee under 37 C.F.R. 1.17(e) is required by 37 C.F.R. 1.114 when the RCE is filed.

a. ☒ The Director is hereby authorized to charge the following fees, or credit any overpayments, to Deposit Account No. 11-0600

i. ☒ RCE fee required under 37 C.F.R. 1.17(e)
ii. ☒ Extension of time fee (37 C.F.R. 1.136 and 1.17)
iii. ☐ Other _____

b. ☐ Check in the amount of $ _____ enclosed

c. ☐ Payment by credit card (Form PTO-2038 enclosed)

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SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Name (Print /Type)	Zeba Ali	*Registration No. (Attorney/Agent)*	51,392
Signature		*Date*	February 1, 2006

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450, or facsimile transmitted to the U.S. Patent and Trademark Office on the date shown below:

Name (Print /Type)			
Signature		*Date*	

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: **Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) FY 2005 *(Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).)*	Docket Number (Optional) **12013/56301**
Application Number **09/542,935**	Filed **April 4, 2000**
For **INSERTABLE OR IMPLANTABLE MEDICAL DEVICES SUITABLE FOR GENE THERAPY REGIMES**	
Art Unit 1635	Examiner B. WHITEMAN

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

	Fee	Small Entity Fee	
☒ One month (37 CFR 1.17(a)(1))	$120	$60	$ 120
☐ Two months (37 CFR 1.17(a)(2))	$450	$225	$_____
☐ Three months (37 CFR 1.17(a)(3))	$1020	$510	$_____
☐ Four months (37 CFR 1.17(a)(4))	$1590	$795	$_____
☐ Five months (37 CFR 1.17(a)(5))	$2160	$1080	$_____

☐ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 11-0600 . I have enclosed a duplicate copy of this sheet.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71

Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

☒ attorney or agent of record. Registration Number 51,392

☐ attorney or agent under 37 CFR 1.34.

Registration number if acting under 37 CFR 1.34. _____ .

Signature	February 1, 2006 Date
Zeba Ali Typed or printed name	202 220 4200 Telephone Number

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☒ Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.136(a). The information is required to obtain or retain a benefit by the public which is to file (and by USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 6 minutes complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED F TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

[Attorney Docket: 12013/56301]

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor : Maria PALASIS	Art Unit : 1635
Serial No.: 09/542,935	Examiner : B. Whiteman
Filing Date: April 4, 2000	
For: Insertable or Implantable Medical Devices Suitable for Gene Therapy Regimens	

MAIL STOP AF
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT UNDER 37 C.F.R. §1.116

SIR:

In response to the Office Action dated July 22, 2005 containing a Final Rejection, Applicants request a one-month extension of time extending the period of response up to and including November 22, 2005. The Office is authorized to charge the one-month extension of time fee to Kenyon & Kenyon's Deposit Account No. 11-0600. Applicants request entry of the following amendments and request reconsideration of the present application. Enclosed herewith is a Notice of Appeal.

Amendments to the Claims:

1-59. (cancelled)

60. (currently amended) A medical device comprising:

a biocompatible structure comprising a polymeric coating that coats at least a portion of said structure, said polymeric coating comprising:

(A) a therapeutic agent, wherein said therapeutic agent ~~selected from the group consisting of~~

~~(1)~~ is an angiogenic agent,

~~(2) an agent that enhances gene transfer and integration into tissue and cells;~~

~~(3) a immunosuppressant;~~

~~(4) an antiangiogenic agent;~~

~~(5) an antithrombogenic agent;~~

~~(6) tissue plasminogen activator;~~

~~(7) erythropoietin;~~

~~(8) an antioxidant;~~

~~(9) an agent blocking smooth muscle proliferation;~~

~~(10) an anti-inflammatory agent;~~

~~(11) a calcium entry blocker;~~

~~(12) an antineoplastic,~~

~~(13) an antiproliferative or anti-mitotic agent;~~

~~(14) an anesthetic agent;~~

~~(15) an anticoagulant;~~

~~(16) an anti-thrombin antibody;~~

~~(17) an anti-platelet receptor antibody;~~

~~(18) a prostaglandin inhibitor;~~

~~(19) a platelet inhibitor;~~

~~(20) a vascular cell growth promoter;~~

~~(21) a growth factor receptor antagonist;~~

~~(22) a transcriptional activator;~~

~~(23) a translational promoter;~~

~~(24) a vascular cell growth inhibitor;~~

~~(25) a growth factor receptor antagonist;~~

~~(26) a transcriptional repressor;~~

~~(27) a translational repressor;~~

~~(28) a replication inhibitor;~~

~~(29) an inhibitory antibody;~~

~~(30) an antibody directed against a growth factor;~~

~~(31) a bifunctional molecule consisting of a growth factor and a cytotoxin;~~

~~(32) a cholesterol lowering agent;~~

~~(33) a vasodilating agent;~~

~~(34) an agent which interferes with endogenous vasoactive mechanisms; and~~

~~(35) a cell cycle inhibitors;~~

and

(B) a vector containing a polynucleotide that establishes a gene expression sufficient to produce a therapeutically sufficient amount of one or more products encoded by said polynucleotide, wherein said polynucleotide encodes a polypeptide or protein, wherein said polypeptide or protein ~~selected from the group consisting of~~

~~(1)~~ is an angiogenic agent~~,~~

~~(2) an antiangiogenic agent;~~

~~(3) an antithrombogenic agent;~~

~~(4) tissue plasminogen activator;~~

~~(5) erythropoietin;~~

~~(6) an antioxidant;~~

~~(7) an agent blocking smooth muscle proliferation;~~

~~(8) an anti-inflammatory agent;~~

~~(9) a calcium entry blocker;~~

~~(10) an antineoplastic,~~

~~(11) an antiproliferative or anti-mitotic agent;~~

~~(12) an anesthetic agent;~~

~~(13) an anticoagulant;~~

~~(14) an anti-thrombin antibody;~~

~~(15) an anti-platelet receptor antibody;~~

~~(16) a prostaglandin inhibitor;~~

~~(17) a platelet inhibitor;~~

~~(18) a vascular cell growth promoter;~~

~~(19) a growth factor receptor antagonist;~~

~~(20) a transcriptional activator;~~

~~(21) a translational promoter;~~

~~(22) a vascular cell growth inhibitor;~~

~~(23) a growth factor receptor antagonist;~~

~~(24) a transcriptional repressor;~~

~~(25) a translational repressor;~~

~~(26) a replication inhibitor;~~

~~(27) an inhibitory antibody;~~

~~(28) an antibody directed against a growth factor;~~

~~(29) a bifunctional molecule consisting of a growth factor and a cytotoxin;~~

~~(30) a cholesterol lowering agent;~~

~~(31) a vasodilating agent;~~

~~(32) an agent which interferes with endogenous vasoactive mechanisms;~~

~~(33) an anti-restenosis agent;~~

~~(34) a monocyte chemoattractant protein;~~

~~(35) a bone morphogenic protein;~~

~~(36) a hedgehog protein and~~

~~(37) a cell cycle inhibitors;~~

~~wherein the angiogenic agent is an acidic fibroblast growth factor, basic fibroblast growth factor, vascular endothelial growth factor, epidermal growth factor, transforming growth factor α and β, platelet derived endothelial growth factor, platelet derived growth factor, tumor necrosis factor α, hepatocyte growth factor, or insulin growth factor~~.

61. (cancelled)

62. (currently amended) A method of controlled delivery of a genetic material to a mammalian body comprising:

(A) applying a polymer coating to at least a portion of a medical device;

(B) applying a genetic material to said polymer coating to obtain a genetically coated medical device, said genetic material comprising:

~~(A)~~ (1) a therapeutic agent, wherein said therapeutic agent ~~selected from the group consisting of~~

~~(1)~~ is an angiogenic agent,

~~(2) an agent that enhances gene transfer and integration into tissue and cells;~~

~~(3) a immunosuppressant;~~

~~(4) an antiangiogenic agent;~~

~~(5) an antithrombogenic agent;~~

~~(6) tissue plasminogen activator;~~

~~(7) erythropoietin;~~

~~(8) an antioxidant;~~

~~(9) an agent blocking smooth muscle proliferation;~~

~~(10) an anti-inflammatory agent;~~

~~(11) a calcium entry blocker;~~

~~(12) an antineoplastic,~~

~~(13) an antiproliferative or anti-mitotic agent;~~

~~(14) an anesthetic agent;~~

~~(15) an anticoagulant;~~

~~(16) an anti-thrombin antibody;~~

~~(17) an anti-platelet receptor antibody;~~

~~(18) a prostaglandin inhibitor;~~

~~(19) a platelet inhibitor;~~

~~(20) a vascular cell growth promoter;~~

~~(21) a growth factor receptor antagonist;~~

~~(22) a transcriptional activator;~~

~~(23) a translational promoter;~~

~~(24) a vascular cell growth inhibitor;~~

~~(25) a growth factor receptor antagonist;~~

~~(26) a transcriptional repressor;~~

~~(27) a translational repressor;~~

~~(28) a replication inhibitor;~~

~~(29) an inhibitory antibody;~~

~~(30) an antibody directed against a growth factor;~~

~~(31) a bifunctional molecule consisting of a growth factor and a cytotoxin;~~

~~(32) a cholesterol lowering agent;~~

~~(33) a vasodilating agent;~~

~~(34) an agent which interferes with endogenous vasoactive mechanisms; and~~

~~(35) a cell cycle inhibitors;~~

and

~~(B)~~ (2) a vector containing a polynucleotide that establishes a gene expression sufficient to produce a therapeutically sufficient amount of one or more products encoded by said polynucleotide, wherein said polynucleotide encodes a polypeptide or protein, wherein said polypeptide or protein ~~selected from the group consisting of~~

~~(1)~~ is an angiogenic agent,

~~(2) an antiangiogenic agent;~~

~~(3) an antithrombogenic agent;~~

~~(4) tissue plasminogen activator;~~

~~(5) erythropoietin;~~

~~(6) an antioxidant;~~

~~(7) an agent blocking smooth muscle proliferation;~~

~~(8) an anti-inflammatory agent;~~

~~(9) a calcium entry blocker;~~

~~(10) an antineoplastic,~~

~~(11) an antiproliferative or anti-mitotic agent;~~

~~(12) an anesthetic agent;~~

~~(13) an anticoagulant;~~

~~(14) an anti-thrombin antibody;~~

~~(15) an anti-platelet receptor antibody;~~

~~(16) a prostaglandin inhibitor;~~

~~(17) a platelet inhibitor;~~

~~(18) a vascular cell growth promoter;~~

~~(19) a growth factor receptor antagonist;~~

~~(20) a transcriptional activator;~~

~~(21) a translational promoter;~~

~~(22) a vascular cell growth inhibitor;~~

~~(23) a growth factor receptor antagonist;~~

~~(24) a transcriptional repressor;~~

~~(25) a translational repressor;~~

~~(26) a replication inhibitor;~~

~~(27) an inhibitory antibody;~~

~~(28) an antibody directed against a growth factor;~~

~~(29) a bifunctional molecule consisting of a growth factor and a cytotoxin;~~

~~(30) a cholesterol lowering agent;~~

~~(31) a vasodilating agent;~~

~~(32) an agent which interferes with endogenous vasoactive mechanisms; and~~

~~a cell cycle inhibitors~~

~~(33) an anti-restenosis agent;~~

~~(34) a monocyte chemoattractant protein;~~

~~(35) a bone morphogenic protein;~~

~~(36) a hedgehog protein and~~

~~(37) a cell cycle inhibitors;~~

~~wherein the angiogenic agent is an acidic fibroblast growth factor, basic fibroblast growth factor, vascular endothelial growth factor, epidermal growth factor, transforming growth factor α and β, platelet derived endothelial growth factor, platelet derived growth factor, tumor necrosis factor α, hepatocyte growth factor, or insulin growth factor;~~ and

(C) inserting or implanting said genetically coated medical device at a predetermined site in said mammal.

63-64. (canceled)

65. (new) The medical device of claim 60, wherein said vector is a viral vector.

66. (new) The medical device of claim 65, wherein said vector is an adenoassociated virus vector.

67. (new) The medical device of claim 60, wherein said polymeric coating comprises polyurethane, silicone, EVA, poly-l-lactic acid /poly ε-caprolactone blends, or a combination thereof.

68. (new) The medical device of claim 60, wherein said polymer coating is from about 1 to about 40 layers having a thickness of from about 1 to about 10 μm/ layer of coating.

69. (new) The medical device of claim 60, wherein said structure is a stent.

70. (new) The medical device of claim 69, wherein said stent is a metallic stent.

71. (new) The medical device of claim 60, wherein said angiogenic agent is acidic or basic fibroblast growth factor.

72. (new) The medical device of claim 60, wherein said angiogenic agent is vascular endothelial growth factor.

73. (new) The medical device of claim 60, wherein said angiogenic agent is platelet-derived growth factor.

74. (new) The medical device of claim 60, wherein said angiogenic agent is platelet-derived endothelial growth factor.

75. (new) The medical device of claim 60, wherein said angiogenic agent is epidermal growth factor.

76. (new) The medical device of claim 60, wherein said angiogenic agent is transforming growth factor α or β.

77. (new) The medical device of claim 60, wherein said angiogenic agent does not include nitric oxide synthase.

78. (new) A method of inhibiting or treating restenosis in a patient, said method comprising administering at a predetermined site within the body of said patient the device of claim 60.

79. (new) The method of claim 78, wherein said site is a site of mechanical injury to an arterial wall produced by treatment of an atherosclerotic lesion by angioplasty.

80. (new) The method of claim 62, wherein said vector is a viral vector.

81. (new) The method of claim 80, wherein said vector is an adenoassociated virus vector.

82. (new) The method of claim 62, wherein said polymeric coating comprises polyurethane, silicone, EVA, poly-l-lactic acid /poly ε-caprolactone blends, or a combination thereof.

83. (new) The method of claim 62, wherein said polymer coating is from about 1 to about 40 layers having a thickness of from about 1 to about 10 μm/ layer of coating.

84. (new) The method of claim 62, wherein said structure is a stent.

85. (new) The method of claim 84, wherein said stent is a metallic stent.

86. (new) The method of claim 62, wherein said angiogenic agent is acidic or basic fibroblast growth factor.

87. (new) The method of claim 62, wherein said angiogenic agent is vascular endothelial growth factor.

88. (new) The method of claim 62, wherein said angiogenic agent is platelet-derived growth factor.

89. (new) The method of claim 62, wherein said angiogenic agent is platelet-derived endothelial growth factor.

90. (new) The method of claim 62, wherein said angiogenic agent is epidermal growth factor.

91. (new) The method of claim 62, wherein said angiogenic agent does not include nitric oxide synthase.

REMARKS

Before this Amendment, claims 3, 10-12, 17-20, 23-25, 27, 34-38, 42-44, 47, 54-55, 58-60, and 62-64 were pending. By this Amendment, claims 3, 10-12, 17-20, 23-25, 27, 34-38, 42-44, 47, 54-55, 58-59, and 63-64 have been canceled and new claims 65-91 have been added. Therefore, if this Amendment is entered, an equal number of dependent claims will have been canceled and added and claims 60, 62, and 65-91 will be pending. It is believed that the added dependent claims all read on the elected species "angiogenic agent." In view of the above, the Applicant submits that it is appropriate to enter this Amendment.

Claims 60 and 62 have been amended to delete the recitation of non-elected species. Claims 60 and 62 now recite a combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent. Support for such a combination is found in the specification, as discussed below in the section directed to the rejections under 35 U.S.C. §112.

Support for new claims 65-91 is as follows:

New claims 65, 66, 67, 68, 69, 70, 78, 79, 80, 81, 82, 83, 84, and 85 correspond to prior claims 10, 3, 17, 18, 19, 20, 24, 25, 34, 27, 42, 43, 44, 47, respectively. These prior claims have been deleted and these new claims added to address the objection in the Office Action that these prior claims did not depend from a preceding claim. New claims 65, 66, 67, 68, 69, 70, 78, 79, 80, 81, 82, 83, 84, and 85 all depend from a preceding claim.

New claims 71-76 and 86-90 recite particular angiogenic agents. Support for the recitation of these particular angiogenic agents is found in the specification as follows:

Claims 71 and 86, page 18, lines 19-20.

Claims 72 and 87, page 18, line 20.

Claims 73 and 88, page 18, line 22.

Claims 74 and 89, page 18, line 21.

Claims 75 and 90, page 18, lines 20-21.

Claim 76, page 18, line 21.

Claims 77 and 91 recite that the angiogenic agent does not include nitric oxide synthase. Support for this recitation is found in the specification, at page 17, line 19 to page 18, line 16, where alternative therapeutic agents are positively recited: "Non-limiting examples of products and therapeutic agents of the invention include: ... nitric oxide synthase (NOS) ..." Such positive recitation nitric oxide as an alternative therapeutic agent provides support for a negative limitation with respect to nitric oxide synthase. See M.P.E.P. §2173.05(i):

> Any negative limitation or exclusionary proviso must have basis in the original disclosure. *If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims.* See *In re Johnson*, 558 F.2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977) ("[the] specification, having described the whole, necessarily described the part remaining."). See also *Ex parte Grasselli*, 231 USPQ 393 (Bd. App. 1983), *aff'd mem.*, 738 F.2d 453 (Fed. Cir. 1984). (Emphasis added)

Election/Restrictions

The Office Action stated that species (2)-(35) and (2)-(37) in claims 60 and 62 were directed to non-elected subject matter.

Claims 60 and 62 have been amended to omit recitation of species (2)-(35) and (2)-(37).

Priority

The Office Action stated that the previous claims are not entitled to the priority date of U.S. Patent Application Serial No. 09/204,254 (now U.S. Patent No. 6,369,039) because "nothing in the specification [of U.S. Patent Application Serial No. 09/204,254] would lead one to the particular combination" of angiogenic agents set forth in the previous claims and therefore U.S. Patent Application Serial No. 09/204,254 lacks a written description of the previous claims (Office Action, paragraph bridging pages 3 and 4).

The claims have been amended to delete recitation of the combination of angiogenic agents recited in the previous claims. All the claims now recite a combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent. To illustrate this, currently amended claim 60 is reproduced below, without the markings showing how it has been amended.

> 60. A medical device comprising:
> a biocompatible structure comprising a polymeric coating that coats at least a portion of said structure, said polymeric coating comprising:
> (A) a therapeutic agent, where said therapeutic agent is an angiogenic agent, and
> (B) a vector containing a polynucleotide that establishes a gene expression sufficient to produce a therapeutically sufficient amount of one or more products encoded by said

polynucleotide, wherein said polynucleotide encodes a polypeptide or protein, where said polypeptide or protein is an angiogenic agent.

The combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent is disclosed in the paragraph at col. 5, l. 49 to col. 6, l. 22 of U.S. Patent No. 6,369,039, which reads in relevant part: "In addition, the polypeptides or proteins that can be incorporated into the polymer coating 130, or whose DNA can be incorporated, include without limitation, angiogenic factors ... and combinations thereof."

The combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent is also disclosed in the paragraph at col.4, l. 64 to col. 5, l. 48. This paragraph teaches which therapeutic agents can be in the coating. Polynucleotides (col. 4, l. 67 to col. 5, l. 4) and angiogenic agents (col. 5, ll. 15-16) are taught. The combination of polynucleotides and angiogenic agents is taught at col. 5, l. 44 ("and combinations thereof"). That the polynucleotides may encode angiogenic agents is taught at col. 5, ll. 62-65.

The present claims are therefore entitled to the priority date of U.S. Patent Application Serial No. 09/204,254 (now U.S. Patent No. 6,369,039).

Claim objections

The claims were objected to because the dependent claims did not depend from a preceding claim.

The claims have been amended so that all dependent claims depend from a preceding claim.

Claims 37 and 58 were objected to as being substantial duplicates.

Claims 37 and 58 have been canceled.

The rejection under 35 U.S.C. §112

The claims were rejected for failure to comply with the written description requirement because the "instant specification does not disclose the subgenus" of angiogenic agents set forth in the claims (Office Action, sentence bridging pages 6-7 and following sentence).

The claims have been amended and no longer recite the subgenus of angiogenic agents to which this rejection was directed. The claims as presently amended have written description support since the specification provides guidance which clearly leads the skilled person to the recited combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent.

The combination of a therapeutic agent comprising genetic material, e.g., a polynucleotide, with a non-genetic therapeutic agent is clearly disclosed at page 17, lines 6-8:

> The first therapeutic agent of this invention comprises genetic materials whereas the second therapeutic agent of the invention may comprise either genetic or non-genetic materials.

The reference to the "first therapeutic agent" in this passage would be understood in light of prior disclosures in the specification which teach that the "first therapeutic agent" is preferably a polynucleotide. See, e.g., page 5, lines 6-7 ("a first therapeutic agent comprising ... a first polynucleotide ..."); page 6, line 9 ("a first therapeutic agent comprising ... a first polynucleotide ..."). Thus, the passage at page 17, lines 6-8 would be understood as teaching the combination of a first therapeutic agent that is a polynucleotide with a non-genetic therapeutic agent.

In the second paragraph after the above disclosure of the combination of a first therapeutic agent that is a polynucleotide with a non-genetic therapeutic agent, there is a disclosure that both therapeutic agents can be angiogenic agents (page 18, line 1).

This is reinforced by original claim 33, which states that "said first therapeutic agent, said second therapeutic agent, ***or both***" can lead to the production of an angiogenic agent. Original claim 33 depends from original claim 26, which, in one of its embodiments, is directed to the combination of a polynucleotide and a protein. Thus, original claim 33 teaches that the Applicant contemplated the combination of a polynucleotide and a protein where the polynucleotide encodes an angiogenic agent and the protein is an angiogenic agent.

The skilled person is again directed to this combination at page 22, line 21 to page 23, line 6, where a preferred embodiment of the invention is disclosed as:

> A preferred embodiment of this invention is to provide treatment of vascular thrombosis and angioplasty restenosis, particularly coronary vascular thrombosis, and angioplasty restenosis, thereby to decrease incidence of vessel rethrombosis and restenosis, unstable angina, myocardial infarction and sudden death. The medical device and method of this invention can be used to treat patients having severe complications resulting from thrombus. Specific examples include patients with acute myocardial infarction (AMI) and patients that have failed PTCA (percutaneous transluminal coronary angioplasty) and have abrupt thrombotic closure of the targeted artery.

From this passage, the skilled person would recognize that the invention is designed to increase blood flow and thereby oxygen delivery to tissues, particularly to tissues sensitive to disruptions in cardiovascular perfusion. The skilled person would recognize that this can be accomplished through a local increase of blood flow by the development and expansion of blood vessels in an area of potential stenosis or thrombotic blockage, i.e., by angiogenesis. Thus, the skilled person is directed to the choice of "angiogenic agents" as the therapeutic agents of the invention.

Furthermore, in Example 7 on pages 28-29, the specification discloses an embodiment in which both therapeutic agents are "angiogenic agents." This example discloses a medical device comprising polynucleotides encoding VEGF protein and FAS Ligand protein.

The specification indicates that VEGF protein is a "promoter of endothelialization" (Example 7, page 29, line 3), i.e., an angiogenic agent. Moreover, it is well known in the art that VEGF protein is known to play a critical and central role in angiogenesis. FAS Ligand is also known to promote angiogenesis. See Biancone et al., Development of Inflammatory Angiogenesis by Local Stimulation of Fas In Vivo. J. Exp. Med. Volume 186, Number 1, July 7, 1997 147-152 (see, e.g., the summary, at page 147: "These findings suggest a role for Fas-Fas ligand interaction in promoting local angiogenesis and inflammation.")

Thus, Example 7 clearly directs the skilled person to the concept of practicing the invention wherein ***both*** therapeutic agents are angiogenic agents. Although Example 7 describes the use of two genetic therapeutic agents rather than the presently claimed combination of a genetic therapeutic agent and a non-genetic therapeutic agent, the combination of a genetic therapeutic agent and a non-genetic therapeutic agent is clearly described elsewhere (see discussion above) and would have been understood as being applicable to the teaching of Example 7 that both therapeutic agents can be angiogenic agents.

In view of the disclosures of the application discussed above, it is clear that the combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent is described in the application. Therefore, the present claims have written description support and it is respectfully requested that this rejection be withdrawn.

The rejection under 35 U.S.C. §102

Certain of the previous claims were rejected as being anticipated by U.S. Patent No. 5,879,713 (Roth).

The Applicant respectfully traverses this rejection. The present claims require a polymeric coating on at least a portion of a medical device. Roth does not disclose a polymeric coating on a medical device. Instead, Roth discloses that a medical device (e.g., a catheter) can be used to deliver a polymer to a tissue so as to form a coating on the surface of the tissue. See col. 11, ll. 43-53:

> Local administration of a polymeric material can be performed by loading the composition in a balloon catheter, and then applying the composition directly to the inside of a tissue lumen within a zone occluded by the catheter balloons. The tissue surface may be an internal or external surface, and can include the interior of a tissue lumen or hollow space whether naturally occurring or occurring as a result of surgery, percutaneous techniques, trauma or disease. The polymeric material can then be reconfigured to form a coating or "paving" layer in intimate and conforming contact with the surface.

The claims have been amended and now recite a combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent. Roth does not disclose this combination. Specifically, although Roth states that biologically active molecules include proteins, nucleic acid molecules, carabohydrates and "combinations thereof," Roth does not describe the specific combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent, as recited by the present claims. Accordingly, Roth does not anticipate the present claims. Thus, it is respectfully requested that this rejection be withdrawn.

The Applicant notes that the present claims are not anticipated by U.S. Patent No. 5,652,225 (Isner). With the exception of one paragraph, the entire disclosure of Isner is directed to the use of hydrophilic polymers incorporating a single DNA encoding a protein, e.g., an angiogenic protein.

The exceptional paragraph occurs at col. 7, ll. 1-10. In this paragraph, Isner describes three additional methods of practicing his invention. The three methods involve certain combinations of DNA encoding angiogenic factors, DNA encoding non-angiogenic factors, angiogenic factors, and non-angiogenic factors.

> In certain situations, it may be desirable to use DNA's [sic] encoding two or more different proteins in order [sic] optimize the therapeutic outcome. For example, DNA encoding two angiogenic proteins, e.g., VEGF and bFGF, can be used, and provides an improvement over the use of bFGF alone. Or an angiogenic factor can be combined with other genes or their encoded gene products to enhance the activity of targeted cells, while simultaneously including angiogenesis, ...

The three methods described in this paragraph are:

Method 1: DNAs encoding two angiogenic proteins, i.e.,

DNA encoding an angiogenic factor + DNA encoding an angiogenic factor

Method 2: an angiogenic factor combined with other genes, i.e.,

An angiogenic factor + DNA encoding a non-angiogenic factor

Method 3: an angiogenic factor combined with gene products of other genes, i.e.,

An angiogenic factor + a non-angiogenic factor

The present claims all require the combination of a polynucleotide (e.g., DNA) encoding an angiogenic agent[1] with an angiogenic agent, i.e., an angiogenic factor + DNA encoding an angiogenic factor.

None of Isner's three methods is directed to an angiogenic factor + DNA encoding an angiogenic factor. This is shown in the following table. In the table, each of the possible combinations of DNA encoding angiogenic factors, DNA encoding non-angiogenic factors, angiogenic factors, and non-angiogenic factors is represented by an entry at the intersection of the corresponding terms at the top and side of the table.

[1] For the purposes of this discussion, it is assumed that the term "angiogenic factor" used by Isner is the same as the term "angiogenic agent" as used in the present claims.

	DNA encoding angiogenic factors	DNA encoding non-angiogenic factors	angiogenic factors	non-angiogenic factors
DNA encoding angiogenic factors	Isner method 1		***The present claims***	
DNA encoding non-angiogenic factors			Isner method 2	
angiogenic factors	***The present claims***	Isner method 2		Isner method 3
non-angiogenic factors			Isner method 3	

It can be seen at a glance that there is no overlap between Isner and the present claims.

Isner goes on to provide a list of some of the products that can be used in his three methods: "including, for example, nitric oxide synthase, L-argine, [sic] fibronectin, urokinase, plasminogen activator and heparin (col. 7, ll. 9-10)."

The Applicant notes that nitric oxide synthase is not an "angiogenic agent" as that term is used in the present application. This can be understood from the manner in which these terms are used in the present application.

• Angiogenic agents and nitric oxide synthase are listed separately in the list of products and therapeutic agents of the invention at page 17, line 20 to page 18, line 17. Angiogenic agents are recited at page 18, line 1 while nitric oxide synthase is recited later, at page 18, line 6, in the midst of anesthetics and anti-coagulants, i.e., products that are undeniably not angiogenic agents. Such listings make no sense if nitric oxide synthase is an angiogenic agent.

• Page 18, line 18 to page 19, line 1, provides a list of angiogenic agents ("acidic and basic fibroblast growth factors, vascular endothelial growth factor, epidermal growth factor, transforming growth factor α and β, platelet-derived endothelial growth factor, platelet-

derived growth factor, tumor necrosis factor α, hepatocyte growth factor and insulin like growth factor"). Nitric oxide synthase is not part of this list.

• Where the present invention provides examples of the use of nitric oxide synthase, nitric oxide synthase is not used an angiogenic agent. Example 6 of the present application (pages 27-28) describes three experiments in which nitric oxide synthase is used for purposes other than angiogenesis (i.e., creating new blood vessels). In experiment 1 (page 27, line 21 to page 28, line 1), nitric oxide synthase is used to prevent restenosis. In experiment 2 (page 28, lines 2-6,), nitric oxide synthase is used to prevent progression and promote the healing of atherosclerotic lesions. In experiment 3 (page 28, lines 7-12), nitric oxide synthase is used to promote cell death in anti-cancer therapy.

Even assuming, *arguendo*, that nitric oxide synthase is considered to be an angiogenic agent by the art, the above teachings of the application make clear that nitric oxide synthase is not an "angiogenic agent" for the purposes of the present invention. The Applicant has been her own lexicographer and has defined the term "angiogenic agent" by implication so as to exclude nitric oxide synthase. Thus, any disclosure of nitric oxide synthase in Isner is not relevant to the present claims.

Even if nitric oxide synthase is considered to be an angiogenic agent, this would not mean that Isner discloses the present invention. If nitric oxide synthase is considered to be an angiogenic agent then it could serve the following roles in the three methods disclosed in Isner:

• either as one or both of the products encoded by the two DNAs of method 1

• as the angiogenic factor that is combined with "other genes" in method 2

• as the angiogenic factor that is combined with the gene products of "other genes" in method 3

In none of these cases would the result be within the scope of the present claims. In no case would the result be an angiogenic agent combined with a DNA encoding an angiogenic agent.

Furthermore, Isner does not anticipate claims 71-76 and 86-90, which are directed to combinations of particular angiogenic agents with DNA encoding those particular angiogenic agents since Isner does not disclose such combinations.

In view of the above, it is clear that Isner does not anticipate the present claims.

The rejections under 35 U.S.C. §103

Certain of the previous claims were rejected as being obvious over Roth taken together with U.S. Patent No. 5,851,521 (Branellec).

The claims have been amended and now recite a combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent. As discussed above, Roth does not disclose this combination. Branellec also does not disclose this combination. Since Roth and Branellec lack a disclosure of this combination, and also lack any suggestion to make this combination, Roth and Branellec do not make obvious the present claims. Thus, it is respectfully requested that this rejection be withdrawn.

Certain of the previous claims were rejected as being obvious over Roth taken together with U.S. Patent No. 5,851,521 (Branellec) and further in view of Vincent-Lacaze et al., 1999, J. Virol. 73:1949-1955 (Vincent-Lacaze).

The claims have been amended and now recite a combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent. As discussed above, Roth and Branellec do not disclose this combination. Vincent-Lacaze also does not disclose this combination. Since Roth, Branellec, and Vincent-Lacaze lack a disclosure of this combination, and also lack any suggestion to make this combination, Roth, Branellec, and Vincent-Lacaze do not make obvious the present claims. Thus, it is respectfully requested that this rejection be withdrawn.

Certain of the previous claims were rejected as being obvious over Roth taken together with U.S. Patent No. 5,833,651 (Donovan).

The claims have been amended and now recite a combination of an angiogenic agent and a polynucleotide encoding an angiogenic agent. As discussed above, Roth does not disclose this combination. Donovan also does not disclose this combination. Since Roth and Donovan lack a disclosure of this combination, and also lack any suggestion to make this combination, Roth and Donovan do not make obvious the present claims. Thus, it is respectfully requested that this rejection be withdrawn.

The Office is authorized to charge any fees or credit any overpayments that may be associated with the filing of this paper to Kenyon & Kenyon's Deposit Account No. 11-0600. The Applicant hereby also makes a Conditional Petition for any relief available to correct any defect seen in connection with this filing, or any defect seen to be remaining in this

application after this filing. The Commissioner is authorized to charge Kenyon & Kenyon's Deposit Account No. 11-0600 for any fees associated with such Conditional Petition.

Respectfully submitted,
KENYON & KENYON

ZEBA Ali for

11-17-05
Date

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/542,935	04/04/2000	Maria Palasis	02844/56301	5876

26646 7590 03/06/2006

KENYON & KENYON LLP
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NEW YORK, NY 10004

EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 03/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/542,935	PALASIS, MARIA	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2006*.

2a)☐ This action is FINAL. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *60,62,65-91* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *60,62,65-91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Non-Final Rejection

Claims 60, 62, and 65-91 are pending.

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 2/1/06 has been entered.

Applicant's traversal, the amendment to claims 60 and 62, and the addition of claims 65-91 is acknowledged and considered by the examiner.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Instant claims 60, 62, and 65-91 are unsupported under 35 U.S.C. 112, first paragraph, as failing to comply with the 112 first paragraph written description.

The original specification (09/204,254 filed 12/3/98, now US 6,369,039) did not disclose making and using a medical device comprising a biocompatible structure carrying a genetic material, said biocompatible structure comprising an angiogenic agent selected from acidic fibroblast growth factor, basic fibroblast growth factor, vascular growth factor, epidermal growth factor, transforming growth factor alpha and beta, platelet-derived growth factor, and platelet-derived growth factor. However, the list set forth in the new claims does not include all of the products listed in the specification that are considered angiogenic agents (e.g., hif-1). The specification does not disclose the subgenus set in the new claims and claims dependent therefrom. Thus, nothing in the specification would lead one to the particular combination set forth in the amended and claims dependent therefrom and new claims. "It is not sufficient for purposes of the written description requirement of Section 112 that the disclosure, when combined with the knowledge in the art, would lead one to speculate as to modifications that the inventor might have envisioned, but failed to disclose." *Lockwood v. American Airlines Inc.*, 41 USPQ2d 1961, 1966 (CAFC 1997).

Thus, the instant claims 3, 10-12, 17-20, 23-25, 27, 34-38, 42-44, 54-55, 58-60 and 62-64 in the application do not enjoy priority to application '254 filed on 12/3/98.

Applicant's arguments filed 9/2/04 have been fully considered but they are not persuasive.

In response to applicant's argument that the original description of the '039 patent provides written description of a therapeutic agent and a vector encoding a polypeptide or protein

selected from the above recited groups, as claimed, the argument is not found persuasive because the applicant selects some polypeptides from the list and excludes other polypeptides in the specification of the '039 patent. See Purdue Pharma L.P. v. Faulding Inc. 230 F.3d 1320, 1326, 56 USPQ2d 1481, 1486 (Fed. Cir. 2000) noting that "with respect In re Ruschig 379 F.2d 990, 154 USPQ 118 (CCPA 1967) that Ruschig makes clear that one cannot disclose a forest in the original application, and then later pick a tree out of the forest and say "here is my invention." In order to satisfy written description requirement, the blaze marks directing the skilled artisan to that tree must be in the originally filed disclosure." This is the case here, the applicant did not disclose using a list of angiogenic agents excluding hif-1, NOS and any other angiogenic agent listed in the instant specification from the subgenus listed in the instant claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 60, 62, and 65-91 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New Matter rejection:

Amended claims 60 and 62 and new claims 65-91 filed on 2/1/06/04 introduce new subject matter into the application.

With respect to the limitation 'a therapeutic agent, wherein said therapeutic agent is an angiogenic agent and a vector containing a polynucleotide that established a gene expression sufficient to produce a therapeutically sufficient amount of one or more products encoded by said polynucleotide, wherein said polynucleotide encodes a polypeptide or protein, wherein said polypeptide or protein is an angiogenic agent' in amended claims 60 and 62 and claims dependent therefrom, the original specification did not disclose the limitation. The asserted support cited for the limitation in the claims does not provide support for the limitation. Page 18, lines 18-22 is directed to the angiogenic agents listed in the dependent claims. However, the specification discloses that either the first or the second polynucleotide or both encode the angiogenic agents. There is no disclosure in the specification of an angiogenic agent and a polynucleotide encoding an angiogenic agent. In addition, page 17, line 20 through page 18, line 16 lists several angiogenic agents that are excluded from the instant claims. The instant specification does not disclose the subgenus set forth in the new claims. It is apparent that the applicants at the time the invention was made did not intend or contemplate making and/or using the medical device set forth in the amended claims and newly added claims as part of the disclosure of their invention. There is no evidence in the specification that the applicants were possession of the medical device as set forth in the newly filed claims and amended claims, as it is now claimed, at the time the application was filed.

Applicant's arguments filed 2/1/06 have been fully considered but they are not persuasive.

In response to applicant's argument that the combination of angiogenic agent and a polynucleotide encoding an angiogenic agent is disclosed in the specification (page 5, lines 6-7 and page 6, line 9), the argument is not found persuasive because both pages are directed to a general description of the claimed invention that does not disclose using a first polynucleotide comprising an angiogenic agent and an angiogenic agent. See *Lockwood v. American Airlines Inc.*,.

In response to the applicant's argument that page 18, line 1 and original claims 26 and 33 provide support for the claimed invention, the argument is not found persuasive because page 18 discloses using a first or second polynucleotide encoding an angiogenic and anti-angiogenic agents and not 1) a polynucleotide encoding an angiogenic agent and 2) an angiogenic protein. This is the same reason for why original claims 26 and 33 do not support the claims.

In response to applicant's argument that in view of page 22, line 21 to page 23, line 6, the skilled person would recognize that the invention was designed to increase blood flow and thereby oxygen delivery to tissues by using "angiogenic agents", the argument is not found persuasive because there is no correlation between using a genus of angiogenic agents and using a particular combination comprising an angiogenic agent and a nucleic acid encoding an angiogenic agent that were not disclosed in the instant specification. See *Lockwood v. American Airlines Inc.*.

In response to applicant's argument that although Example 7 on pages 28-29 discloses using two genetic therapeutic agents, the Example clearly directs the skilled person to the concept of practicing the invention wherein both therapeutic agents are "angiogenic agents", the argument is not found persuasive because there is no correlation between using a genus of

angiogenic agents and using an angiogenic agent and a nucleic acid encoding an angiogenic agents. See Purdue Pharma L.P. v. Faulding Inc. 230 F.3d 1320, 1326, 56 USPQ2d 1481, 1486 (Fed. Cir. 2000).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 60, 62, 65, 67, 68, 69, 71, 72, 73. 75, 77-80, 82-84, 86, 87, 88, 90, and 91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roth (US 5,879,713) taken with Crystal et al. (US 5,869,037). Roth teaches delivering to a vascular system of an animal a biodegradable, biocompatible polymeric microparticles comprising biologically active molecules selected from the group consisting of growth factors, cytokines, angiogenesis factors, immunosuppressant molecules, peptide fragments thereof and nucleic acid constructs capable of synthesizing these compounds, wherein restenosis has occurred following balloon angioplasty

(abstract and columns 10 and 16-18). Roth teaches the limitation in instant claims 78 and 79 (columns 10 and 16-18). The growth factors can be VEGF, bFGF, and PDGF and DNA encoding them (column 10). The biologically active molecules, which are immobilized on the polymeric microparticles can include proteins, nucleic acid molecules, carbohydrates, lipids and combinations thereof (column 9). Roth teaches the limitation in instant claim 67 (columns 3-4). Roth teaches the limitation in instant claim 68 (column 11). Roth teaches the limitation in instant claims 69 and 84 (column 11). However, Roth does not specifically teach using a nucleic acid encoding an angiogenic agent and an angiogenic agent in the microparticles.

However, at the time the invention was made, Crystal teaches composition comprising a viral vector comprising a nucleic acid encoding a VEGF polypeptide (column 11). Crystal teaches that the composition can be formulated into preparations in solids (column 11). Crystal further teaches that the vector can be delivered with other means of stimulating angiogenesis such as treatment with other angiogenic growth factors (column 11). One of ordinary skill in the art understands that adenovirus provides an efficient means for transferring biological materials to target cells (columns 1 and 2).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Roth taken with Crystal, namely to produce a medical device comprising a polymeric coating comprising a vector comprising a polynucleotide encoding an angiogenic agent and an angiogenic agent. One of ordinary skill in the art would have been motivated to combine the teaching to enhance the circulation where there has been vascular occlusion. See also In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Roth taken with Crystal, namely to use the medical device to treat restenosis in a patient. One of ordinary skill in the art would have been motivated to combine the teaching to deliver the agents in a controlled and sustained manner as exemplified by Roth (column 2).

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Roth taken with Crystal, namely to use an adenovirus in the medical device for treating a patient with restenosis. One of ordinary skill in the art would have been motivated to combine the teaching to improve the delivery of the nucleic acid to the cells of interest as exemplified by Crystal (columns 1 and 2).

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

In response to applicant's argument that Roth does not disclose a polymeric coating on a medical device, the argument is not found persuasive because Roth teaches loading the polymeric coating comprising the therapeutic agents onto a stent, which would indicate to the skilled artisan that the teaching of Roth would read on coating on a medical device.

Applicant's arguments with respect to claims 67, 68, 69, 71, 72, 73, 75, 77-80, 82-84, 86, 87, 88, 90, and 91 have been considered but are moot in view of the new ground(s) of rejection.

Claims 60, 62, 65, 66, 80, and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roth et al. taken with Crystal et al. as applied to claims 60, 62, 65, 67, 68, 69,

71, 72, 73, 75, 77-80, 82-84, 86, 87, 88, 90, and 91 above, in further view of Branellec et al. (US Patent No. 5,851,521, cited on a previous PTO-892).

However; Roth and Crystal do not specifically making and using a viral vector (AAV) to deliver the nucleic acid.

However, at the time the invention was made, replication defective AAV viral vectors were well known to one of ordinary skill in the art for delivering nucleic acid to cells using a catheter and using micro-particles (e.g. polylactide) to deliver said nucleic acid (column 9, line 60-column, line 67). Branellec teaches using AAV vectors comprising a protein in a method inhibiting restenosis in a mammal (abstract and column 7, lines 55-65). AAV vectors are able to infect a wide spectrum of cells without inducing any effect on cellular growth, morphology, or differentiation and they do not appear to be involved in human pathologies.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Roth taken with Crystal in further view of Branellec, namely to produce the microparticle comprising a replication defective AAV vector. One of ordinary skill in the art would have been motivated to combine the teaching and make the microparticle comprising a replication defective AAV vector because AAV vectors are well known to one of ordinary skill in the art to be non-pathogenic in vivo and infect a wide spectrum of cells without inducing any effect on cellular growth, morphology, or differentiation.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Roth taken with Crystal in further view of Branellec, namely to use a replication defective AAV vector in the microparticle for delivering a genetic material to a mammal. One of ordinary skill in the art would have been

motivated to combine the teaching and use the replication defective AAV in the method because AAV vectors are non-pathogenic in mammals and are well known to one of ordinary skill in the art for delivering a nucleic acid to a mammal with restenosis as exemplified by Branellec (column 7).

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments with respect to claims 60 and 62 have been considered but are moot in view of the new ground(s) of rejection.

Claims 60, 62, 69, 70, 84, and 85 are rejected under 35 U.S.C. 103(a) as being unpatentable Roth et al. taken with Crystal et al. as applied to claims 60, 62, 65, 67, 68, 69, 71, 72, 73, 75, 77-80, 82-84, 86, 87, 88, 90, and 91 above, and further in view of with Donovan et al. (US 5,833,651, cited on a previous PTO-892).

However, Roth and Crystal do not specifically making and using a metallic stent to deliver the vector and the angiogenic agent.

However, at the time the invention was made, Donovan teaches that metallic stents are well known to one of ordinary skill in the art for delivering microparticles to an area of a mammal (columns 5-6).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Roth taken with Crystal in further view of Donovan, to make a metallic stent comprising the microparticle. One of ordinary skill in the art would have been motivated to combine the teaching, as a matter of designer's choice, and make

a metallic stent comprising the microparticle because metallic stents are well known to one of ordinary skill in the art for delivering a microparticle to an area of a mammal as exemplified by Donovan (columns 5-6).

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Roth taken with Crystal in further view of Donovan, namely to use a metallic stent for delivering the microparticle to an area of a mammal. One of ordinary skill in the art, as a matter of designer's choice, would have been motivated to combine the teaching and use a metallic stent in the method because metallic stents are well known to one of ordinary skill in the art for sustainable delivery of microparticles to an area of a mammal as exemplified by Donovan (columns 5-6).

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments with respect to claims 60 and 62 have been considered but are moot in view of the new ground(s) of rejection.

Claims 60, 62, 74, 76, and 89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roth taken with Crystal as applied to claims 60, 62, 65, 67, 68, 69, 71, 72, 73, 75, 77-80, 82-84, 86, 87, 88, 90, and 91 above, and further in view of Isner (US 5,652,225).

However, Roth taken with Crystal do not specifically teach using PEGF and TGF alpha or TGF beta.

However, at the time the invention was made, PEGF, TGF-alpha and TGF beta were known to one of ordinary skill in the art as angiogenic proteins as taught by Isner. See column 3.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Roth and Crystal in further view of Isner, namely to use PEGF in the method. One of ordinary skill in the art would have been motivated to combine the teaching because PEGF is a growth factor that can be used to induce angiogenesis in a patient.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Roth and Crystal in further view of Isner, namely to use either TGF alpha or TGF beta in the method. One of ordinary skill in the art would have been motivated to combine the teaching because TGF alpha and TGF beta are growth factors that can be used to induce angiogenesis in a patient.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments with respect to claims 60 and 62 have been considered but are moot in view of the new ground(s) of rejection.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, acting SPE – Art Unit 1635, can be reached at (571) 272-0811.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center number is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Brian Whiteman
Patent Examiner, Group 1635

B. Whiteman

BRIAN WHITEMAN
PATENT EXAMINER

Notice of References Cited	Application/Control No. 09/542,935	Applicant(s)/Patent Under Reexamination PALASIS, MARIA	
	Examiner Brian Whiteman	Art Unit 1635	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-5,869,037	02-1999	Crystal et al.	424/93.2
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.